DDM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 101

Display Date 1-4-06 7
Publication Date 1-5-06 7
Certifier A. Corbin

[Docket No. 2004P–0464]

Food Labeling: Health Claims; Calcium and Osteoporosis, and Calcium, Vitamin D, and Osteoporosis

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the regulation authorizing a health claim on the relationship between calcium and a reduced risk of osteoporosis to: Include vitamin D so that, in addition to claims for calcium and osteoporosis, additional claims can be made for calcium and vitamin D and osteoporosis; eliminate the requirement in § 101.72(c)(2)(i)(A) (21 CFR 101.72(c)(2)(i)(A)) that the claim list sex, race, and age as specific risk factors for the development of osteoporosis; eliminate the requirement in § 101.72(c)(2)(i)(B) that the claim does not state or imply that the risk of osteoporosis is equally applicable to the general U.S. population, and that the claim identify the populations at particular risk for the development of osteoporosis; eliminate the requirement in § 101.72(c)(2)(i)(C) that the claim identify the mechanism by which calcium reduces the risk of osteoporosis and instead make it optional; and eliminate the requirement in § 101.72(c)(2)(i)(E) that the claim include a statement that reflects the limit of the benefits derived from dietary calcium intake, when the level of calcium in the food exceeds a set threshold level. FDA is taking these actions, in part,

cf0540 2004P-0464

NPR 1

in response to a health claim petition submitted by The Beverage Institute for Health and Wellness, LLC. Elsewhere in this issue of the **Federal Register**, FDA is withdrawing certain proposed amendments to a proposed rule that published in the **Federal Register** of December 21, 1995 (60 FR 66206) related to the calcium and osteoporosis health claim.

DATES: Submit written or electronic comments by [*insert date 75 days after date of publication in the* **Federal Register**].

ADDRESSES: You may submit comments, identified by Docket No. 2004P–0464, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following ways:

- Federal eRulemaking Portal: *http://www.regulations.gov*. Follow the instructions for submitting comments.
- Agency Web site: *http://www.fda.gov/dockets/ecomments*. Follow the instructions for submitting comments on the agency Web site.

Written Submissions

Submit written submissions in the following ways:

- FAX: 301–827–6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD–ROM submissions]: Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal or the agency Web site, as described in the *Electronic Submissions* portion of this paragraph.

Instructions: All submissions received must include the agency name and Docket No(s). and Regulatory Information Number (RIN) (if a RIN number has been assigned) for this rulemaking. All comments received may be posted without change to *http://www.fda.gov/ohrms/dockets/default.htm*, including any personal information provided. For additional information on submitting comments, see the "Comments" heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.fda.gov/ohrms/dockets/default.htm* and insert the docket number(s), found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Jillonne Kevala, Center for Food Safety and Applied Nutrition (HFS–830), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740–3835, 301–436–1450.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Background

II. Petition and Grounds for Amending the Health Claim on Calcium and Osteoporosis

A. The Petition

B. Nature of the Substance

III. Review of Scientific Evidence of the Substance-Disease Relationship

A. Basis for Evaluating the Relationship between Calcium and Vitamin D and Osteoporosis

B. Review of the Scientific Evidence of the Substance-Disease Relationship

IV. Decision to Amend the Calcium and Osteoporosis Health Claim

A. Addition of Vitamin D

B. Amendments to the Calcium and Osteoporosis Health Claim Other than the Inclusion of Vitamin D

C. Elimination of the Requirement to List Race, Age and Sex as Risk Factors for the Development of Osteoporosis

D. Elimination of the Requirement that the Claim Not State or Imply that the Risk of Osteoporosis is Equally Applicable to the General Population, and that the Claim Identify the Populations at Particular Risk for the Development of Osteoporosis

E. Elimination of the Requirement that the Claim Identify the Mechanism by Which Calcium Reduces the Risk of Osteoporosis

F. Elimination of the Requirement in § 101.72(c)(2)(i)(E) that Certain Products Bearing the Claim Include a Statement that Reflects the Limits on the Benefits from Calcium

V. Description of Modifications to § 101.72

A. Title of the Regulation

B. General Requirements

VI. Analysis of Economic Impacts

A. Preliminary Regulatory Impact Analysis

B. Small Entity Analysis (or Initial Regulatory Flexibility Analysis)

VII. Environmental Impact

VIII. Paperwork Reduction Act

IX. Federalism

X. Comments

XI. References

I. Background

The Nutrition Labeling and Education Act of 1990 (NLEA) (Public Law 101–535) amended the Federal Food, Drug, and Cosmetic Act (the act) in a number of important ways. The NLEA clarified FDA's authority to regulate health claims on food labels and in food labeling by amending the act to add section 403(r) to the act (21 U.S.C. 343(r)). Section 403(r) specifies, in part, that a food is misbranded if it bears a claim that expressly or by implication characterizes the relationship of a nutrient to a disease or health-related condition unless the claim is made in accordance with section 403(r)(3) (for conventional foods) or 403(r)(5)(D) (for dietary supplements).

The NLEA directed FDA to issue regulations authorizing health claims (i.e., labeling claims that characterize the relationship of a substance to a disease or health-related condition) for conventional foods only if the agency determines, based upon the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles), that there is significant scientific agreement (SSA), among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence (21 U.S.C. 343(r)(3)(B)(i)). Congress delegated to FDA the authority to establish the procedure and standard for health claims for dietary supplements (21 U.S.C. 343(r)(5)(D)).

FDA issued regulations establishing general requirements for health claims in labeling for conventional foods (58 FR 2478; January 6, 1993). By regulation (59 FR 395; January 4, 1994), and under Congressional authority,[1] FDA adopted the same general requirements, including the procedure and standard, for

[1]FDA issued regulations establishing general requirements for health claims in dietary supplement labeling (59 FR 395) under the NLEA and the Dietary Supplement Act of 1992 (Public Law 102–571).

health claims in dietary supplement labeling that Congress had prescribed in the NLEA for health claims in the labeling of conventional foods. (See 21 U.S.C. 343(r)(3) and (r)(4)).

The regulations require the evidence supporting a health claim to be presented to FDA for review before the claim may appear in labeling (§§ 101.14(d) and (e) and 101.70 (21 CFR 101.14(d) and (e) and 21 CFR 101.70)). The standard requires a finding of "significant scientific agreement" (SSA) before FDA may authorize a health claim by regulation (§ 101.14(c)).

Among its provisions regulating claims, the NLEA required FDA to determine whether claims respecting 10 specific substance/disease relationships met the requirements for a health claim (NLEA section 3(b)(1)(A)(vi) and (x), Public Law 101–535). The relationship between calcium and a reduced risk of osteoporosis was one of those 10 nutrient/disease relationships. On March 28, 1991, FDA published a notice in the **Federal Register** requesting scientific data and information on the 10 specific topic areas identified (56 FR 12932). Scientific studies and data received in response to the notice, that were relevant to the agency's review, were considered as part of the agency's review of the scientific literature on calcium and osteoporosis and were included in the proposed rule for the calcium and osteoporosis health claim for use on foods, including dietary supplements (56 FR 60689; November 27, 1991) (the 1991 proposed rule). Before publication of the calcium and osteoporosis final rule (58 FR 2665; January 6, 1993), the agency reviewed any scientific research and review articles relevant to calcium intake and osteoporosis that became available after publication of the proposed rule and concluded that the new studies were consistent with the tentative conclusions drawn in the 1991 proposed rule (58 FR 2665 at 2672). Thus, in

the calcium and osteoporosis final rule FDA concluded that, based on the totality of the publicly available scientific evidence, there was significant scientific agreement among qualified experts that a health claim for calcium and a reduced risk of osteoporosis was supported by the evidence (id.) (Codified in § 101.72 (21 CFR 101.72)).

In December of 1995, in response to citizen petitions submitted by the National Food Processors Association (Docket No. 1994P–0390) and the American Bakers Association (Docket No. 1995P–0241), FDA proposed to amend its regulations on health claims and nutrient content claims to provide more flexibility in the use of these claims on food products (60 FR 66206; December 21, 1995) (the 1995 proposal). This document discussed many proposed amendments to FDA regulations intended to benefit public health by encouraging manufacturers to use health claims and nutrient content claims to assist consumers in maintaining healthy dietary practices. In the 1995 proposal, FDA proposed, among other things, certain amendments to simplify the current required claim language for the calcium and osteoporosis health claim in § 101.72.

In response to requests by stakeholders and other FDA initiatives and developments, the agency reopened the comment period for the 1995 proposal several times. The most recent reopening of the comment period was announced in the **Federal Register** on May 4, 2004 (69 FR 24541), and the comment period was open until July 6, 2004. Because many of the amendments in the 1995 proposal are similar to or exactly the same as those requested by The Beverage Institute for Health and Wellness in their health claim petition, and that FDA is proposing herein, the agency considered the comments submitted in response to the 1995 proposal in the development of this

proposed rule. Comments on other aspects of the 1995 proposal are not considered in this proposed rule. Elsewhere in this issue of the **Federal Register**, the agency is withdrawing the part of the 1995 proposed rule related to the calcium and osteoporosis claim language.

II. Petition and Grounds for Amending the Health Claim on Calcium and Osteoporosis

A. The Petition

On July 12, 2004, the agency received a health claim petition submitted by The Beverage Institute for Health and Wellness (the petitioner) under section 403(r)(4) of the act.[2] The petitioner noted that the agency already has an authorized health claim (§ 101.72) on the ability of calcium to reduce the risk of osteoporosis among teen and young adult white and Asian women who engage in regular physical activity, and stated that they believed that there was now significant scientific agreement to support authorization of an expanded osteoporosis health claim that includes vitamin D and eliminates the restrictive language regarding age, race, gender, and physical activity. The petitioner also noted that FDA had already proposed most of the petitioner's proposed amendments in the 1995 proposal (60 FR 66206).

Specifically, the petitioner's proposed amendments to § 101.72 would: (1) Include vitamin D so that, in addition to claims for calcium and osteoporosis, additional claims can be made for calcium and vitamin D and osteoporosis; (2) eliminate the required claim language in § 101.72(c)(2)(i)(A) regarding race, age, gender, and the need for physical activity; (3) eliminate the requirement in § 101.72(c)(2)(i)(B) that the claim identify the population at particular risk

[2]Although the petitioner cited only section 403(r)(4) of the act, which applies to the use of the claim on conventional foods, the agency is including within its review the use of the claim in dietary supplement labeling under section 403(r)(5)(D) of the act. This is consistent with the calcium and osteoporosis health claim in § 101.72, which applies to both conventional food and dietary supplements.

for osteoporosis; (4) eliminate the requirement in § 101.72(c)(2)(i)(C) that the claim identify the mechanism by which calcium reduces the risk of osteoporosis and instead make this information optional; (5) simplify the language used in the claim; and (6) increase the amount of calcium present in the food (from 400 milligrams (mg) of calcium per reference amount customarily consumed or per daily recommended supplement intake to more than 1,500 mg calcium per day) before the claim must include a statement that reflects the limit on the benefit derived from dietary calcium intake. The petitioner concluded that amending the osteoporosis and calcium health claim in the above manner would provide the availability of a simplified, understandable health claim that would allow food manufacturers to help address the public health issue of osteoporosis by educating consumers about the importance of both vitamin D and calcium in reducing the risk of osteoporosis in later life (Ref. 1). Finally, the petitioner requested that the agency exercise its authority under section 403(r)(7) of the act to make any proposed regulation based on their petition effective upon publication, pending consideration of public comment and publication of a final rule.

On October 20, 2004, we notified the petitioner that we had completed our initial review of the petition and that the petition had been filed for further action (Docket No. 2004P–0464, Let 1) in accordance with section 403(r)(4) of the act. The October 20, 2004, letter stated that if the agency did not act, by either denying the petition or issuing a proposed regulation to authorize the health claim, within 90 days of the date of filing, the petition would be deemed to be denied unless an extension was mutually agreed upon by the agency and the petitioner (section 403(r)(4)(A)(i) of the act and

§ 101.70(j)(3)(iii)). FDA and the petitioner agreed to extend the publication date of a regulation until January 18, 2007 (Docket No. 2004P–0464, Let 6).

B. Nature of the Substance

The petition requested, among other things, that FDA amend the calcium and osteoporosis health claim (§ 101.72) to include vitamin D so that, in addition to claims for calcium and osteoporosis, claims can be made for calcium and vitamin D and osteoporosis. Thus, FDA considered two substances that are the subject of the petition: (1) Calcium and (2) calcium and vitamin D. Unless specified, the term 'vitamin' D means D_2 (ergocalciferol), D_3 (cholecalciferol) or a combination of vitamin D_2 and D_3.

C. Review of the Preliminary Requirements

1. The Substance is Associated With a Disease for Which the U.S. Population is at Risk

Osteoporosis, which is defined as a skeletal disorder characterized by compromised bone strength, continues to be a major public health problem in the United States, even after authorization of the calcium and osteoporosis health claim in 1993. The continued public health problem is reflected, in part, by the observation that the number of bone fractures in the United States has increased as well as the direct medical costs required to treat osteoporosis (Ref. 2). The petitioner stated that in 2002 the National Osteoporosis Foundation estimated that approximately 44 million men and women in the United States had low bone density or osteoporosis and that this value was projected to increase to more than 61 million by 2020 (Ref. 3). White and Asian women are the most susceptible to chronic bone disease, but the petitioner noted that the condition was also prevalent among African Americans (Ref. 3). Five

percent of the African American U.S. population (more than 13 million people) are currently thought to have osteoporosis compared to 20 percent for White and Asian women (Ref. 3). The incidence of low bone mineral density in 2002 for African Americans and White and Asian women was estimated to be 35 and 52 percent, respectively (Ref. 3). The direct care expenditures resulting from osteoporosis range from 12.2 to 17.9 billion dollars each year measured in 2002 dollars (Ref. 4).

FDA agrees with the petitioner that, as required in § 101.14(b)(1), osteoporosis is a disease for which the U.S. population is at risk.

2. The Substances are Components of Food

A health claim characterizes the relationship between a substance and a disease or a health-related condition (§ 101.14(a)(1)). A substance means a specific food or a component of food, regardless of whether the food is in conventional food form or a dietary supplement (§ 101.14(a)(2)). The petition identified calcium and vitamin D as a new substance for consideration in the calcium and osteoporosis health claim. Calcium, one of the essential nutrients for humans, is a component of milk and milk products (approximately 300 mg per serving), as well as other food sources (e.g., Chinese cabbage, kale, and broccoli) (Ref. 5). Vitamin D is naturally present in a small number of foods, such as some fish liver oils, the flesh of fatty fish, the liver and fat from aquatic mammals such as polar bears and seals, and eggs from hens that have been fed vitamin D (Ref. 6). Therefore, the agency concludes that calcium and vitamin D, are components of food and meet the definition of a substance in the health claim regulation.

Health claim general requirements provide that where a substance is to be consumed at "other than decreased dietary levels" the substance must

contribute taste, aroma, or nutritive value, or any other technical effect listed in 21 CFR 170.3(o), and must retain that attribute when consumed at levels necessary to justify the claim (§ 101.14(b)(3)(i)). Nutritive value as defined in § 101.14(a)(3) means a value in sustaining human existence by such processes as promoting growth, replacing loss of essential nutrients, or providing energy. Calcium and vitamin D are essential nutrients and thus provide nutritive value to the diet (Refs. 5 and 6) and retain that attribute when consumed at levels necessary to justify the claim. Therefore, FDA concludes that the requirement of § 101.14(b)(3)(i) is satisfied.

3. The Substances are Safe and Lawful

Under § 101.14(b)(3)(ii), if the substance is to be consumed at other than decreased dietary levels, the substance must be a food or a food ingredient whose use at levels necessary to justify a claim has been demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under the applicable food safety provisions of the act.

FDA evaluates whether the substance is "safe and lawful" under the applicable food safety provisions of the act. For conventional foods, this evaluation involves considering whether the ingredient that is the source of the substance is generally recognized as safe (GRAS), approved as a food additive, or authorized by a prior sanction issued by FDA. (See § 101.70(f).)

Dietary ingredients in dietary supplements are not subject to the food additive provisions of the act (see section 201(s)(6) of the act (21 U.S.C. 321(s)(6)). Rather, they are subject to the adulteration provisions in section 402 of the act (21 U.S.C. 342) and, if applicable, the new dietary ingredient provisions in section 413 of the act (21 U.S.C. 350b), which pertain to dietary ingredients that were not marketed in the United States before October 15,

1994. The term "dietary supplement" is defined in section 201(ff)(1) of the act and includes vitamins; minerals; herbs and other botanicals; dietary substances for use by man to supplement the diet by increasing total daily intake; and concentrates, metabolites, constituents, extracts, and combinations of the preceding types of ingredients.

For dietary supplements, the applicable safety provisions require, among other things, that the dietary ingredient not present a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling or, if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use (section 402(f)(1)(A) of the act). Further, a dietary supplement must not contain a poisonous or deleterious substance which may render the supplement injurious to health under the conditions of use recommended or suggested in the labeling (section 402(f)(1)(D) of the act).

The use of a health claim for calcium, or calcium and vitamin D, and osteoporosis is being evaluated for use on the labels and in the labeling of both conventional foods and dietary supplements. Thus, the agency is evaluating the safety and lawfulness of both calcium and vitamin D under the relevant provisions of the act for both conventional foods and for dietary supplements.

a. *Vitamin D*

The petitioner asserts that vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol) have been affirmed as GRAS when used as a source of this nutrient for breakfast cereals, grain products and pastas, milk, and milk products according to § 184.1950(c)(1) (21 CFR 184.1950(c)(1)). Vitamin D may also be added to infant formula in accordance with section 412(a)(2) of the

act (21 U.S.C. 350a(a)(2)), and as an optional ingredient in margarine according to § 166.110 (21 CFR 166.110). The petitioner also asserts that FDA recently approved vitamin D_3 as a food additive that may be added in amounts up to 100 International Units (IU) per serving to 100 percent fruit juices (excluding those specifically formulated for infants) that are fortified with greater than 33 percent of the Reference Daily Intake (RDI) of calcium per reference amount customarily consumed (RACC) and to fruit drinks (excluding those specifically formulated for infants) that are fortified with greater than 10 percent of the RDI of calcium per RACC (68 FR 9000; February 27, 2003). As part of that rulemaking, FDA determined that persons 1 year of age or older would not be exposed to amounts of vitamin D greater than the Tolerable Upper Intake Levels (UL) after fortification of eligible juice products (68 FR 9000 at 9002). However, the agency did not allow vitamin D fortification of juice products specifically formulated for infants (id.). Thus, FDA concluded that the addition of vitamin D_3 to calcium-fortified fruit juices and juice drinks, excluding fruit juices and juice drinks specifically formulated or processed for infants, at levels not to exceed 100 IU per RACC is safe (68 FR 9000 at 9002).

FDA acknowledges that vitamin D_2 and vitamin D_3 have been affirmed as GRAS when used in breakfast cereals, grain products, pastas, milk and milk products at the intended levels (§ 184.1950) and that vitamin D_3 has been approved as a food additive to calcium-fortified 100 percent fruit juice and fruit drinks not intended for infants ((§ 172.380) (21 CFR 172.380)). FDA also acknowledges that vitamin D may be added to infant formulas in accordance with section 412(a)(2) of the act and to margarine as an optional ingredient (§ 166.110). Thus, the agency is satisfied that the petitioner has demonstrated

that vitamin D may be lawfully used in conventional foods for the specific uses cited.

UL, as defined by the Institute of Medicine (IOM), are the highest levels of daily nutrient intake that are likely to pose no risks of adverse effects to almost all individuals in the general population (Ref. 7). The IOM has established a UL for vitamin D by life stage, gender, and age (Ref. 6). The IOM concluded that the most biologically important possible adverse effect of excessive vitamin D is hypercalcemia (i.e., an abnormally high concentration of calcium compounds in the circulating blood) due to hypervitaminosis D. Hypervitaminosis D is a condition resulting from the ingestion of an excessive amount of the fat-soluble vitamin D. Using hypercalcemia as the clinically defined endpoint, the IOM identified a no-observed-adverse-effect level (NOAEL) at 2,400 IU per day for adults. The IOM established 2,000 IU of vitamin D as the UL for individuals older than 18 years by dividing the NOAEL by an uncertainty factor of 1.2 to be conservative to account for uncertainties in the data set. The UL for individuals 1 through 18 years and pregnant and lactating women is specified as 2,000 IU per day (Ref. 6).

The most recent nationally representative data, 1988-1994 National Health and Nutrition Examination Survey (NHANES), found that the median intake vitamin D intake from foods, excluding dietary supplements, to be 164 IU/day for all individuals aged 2 months and older, excluding nursing infants (Ref. 8). Vitamin D can be obtained from dietary supplement sources as well as other food sources. Results from the NHANES 1988-1994 survey indicate that approximately 40 percent of the U.S. population, ages 2 months or older take dietary supplements and that the most frequent amount of vitamin D taken as a dietary supplement is 400 IU/day (Ref. 9).

Supplemental vitamin D can be obtained from multiple vitamin and mineral products, products where calcium and vitamin D are the only ingredients, or products where vitamin D is the sole ingredient (Ref. 9). Supplemental vitamin D can also be obtained from fish liver oils, such as cod liver oil (Ref. 10). Multiple vitamin and mineral supplement products generally contain 200 or 400 IU of vitamin D per RACC and recommend consumption of 1 serving per day. The RACC for dietary supplements is the maximum amount recommended as appropriate on the label for consumption per eating occasion, or in the absence of recommendations, one unit (i.e., one tablet, one capsule, one packet, one teaspoon etc. (see § 101.12(b) (21 CFR 101.12(b)) Table 2.—Reference Amounts Customarily Consumed Per Eating Occasion: General Food Supply [1, 2, 3, 4] (Table 2)). Calcium and vitamin D only products generally contain between 100 to 600 IU of vitamin D per RACC (Ref. 11). Calcium and vitamin D only products with a RACC of less than 400 IU of vitamin D recommend consumption of one to three servings per day and the recommended vitamin D intake does not exceed 600 IU per day. Calcium and vitamin D only products with an RACC of 400 IU of vitamin D or more recommend consumption of 1 serving per day and the recommended vitamin D intake does not exceed 1,000 IU per day (id.). Supplements that contain only vitamin D generally contain 400 to 1,000 IU per RACC, and recommend consumption of 1 serving per day (id). Cod liver oil products contain between 100 to 540 IU of vitamin D per RACC and the recommended vitamin D intake does not exceed 1,000 IU per day in these products (id.). Thus, the range of vitamin D intake from the various types of dietary supplement products generally varies from 100 to 1,000 IU/day. Only 7 percent of the products surveyed recommend consumption of 1,000 IU of vitamin D per day (id).

FDA has also considered the intake of vitamin D from food and dietary supplements among consumers of fruit juices and juice drinks, as part of its rulemaking in response to a food additive petition for vitamin D_3 (68 FR 9000). Relying on data submitted by the petitioner for consumers of fruit juices and juice drinks 2 years of age and older, it was estimated that the average and 90th percentile dietary intakes from currently regulated uses in conventional foods (including naturally occurring sources) and proposed food uses of vitamin D, were 306 IU per person per day (IU/p/d) and 519 IU/p/d, respectively (68 FR 9000 at 9001). Taking into account that the most frequent level of vitamin D taken as a dietary supplement is 400 IU/day, FDA estimated the mean and 90th percentile dietary intakes for consumers of fruit juices and juice drinks 2 years of age and older from current and proposed food uses and dietary supplement uses were 706 IU/p/d and 919 IU/p/d, respectively (id.). Thus, the mean and 90th percentile vitamin D intake for this population of consumers is also well below the UL of 2,000 IU/day.

The petitioner is proposing that for a food to be eligible for the additional calcium and vitamin D and osteoporosis health claim that the food meet or exceed the requirements for a "high" level of calcium and a "high" level for vitamin D, as "high" is defined in § 101.54 (21 CFR 101.54), as the levels necessary to justify the health claim. For a food to be labelled as "high" in vitamin D, it must contain 20 percent or more of the RDI per RACC for the specified nutrient. The RDI for vitamin D is 400 IU. Twenty percent of the RDI for vitamin D per day is 80 IU.

FDA notes that certain prepared foods are subject to food additive regulations that limit the amount of vitamin D that can be added to such foods. As noted previously, § 184.1950 allows the addition of vitamin D to breakfast

cereals (350 IU/100 g), grain products and pastas (90 IU/100 g), milk (42 IU/ 100g) and milk products (89 IU/100 g). In addition, § 166.110 permits fortification of margarine (330 IU/100 g) and the newly issued § 172.380 permits the addition of vitamin D_3 to calcium-fortified 100 percent fruit juice and fruit drinks not intended for infants (100 IU/serving). Of these foods, those that are "high" in calcium (i.e., milk, certain milk products, fortified breakfast cereals and juices) are permitted to add enough vitamin D to be "high" in vitamin D to qualify for the additional claim. Foods that are not "high" in calcium (e.g., margarine, enriched grain products and pastas) would not be permitted to bear the calcium only claim. Likewise, these foods would not be permitted to bear the calcium and vitamin D and osteoporosis claim because both calcium and vitamin D must each be present at "high" levels to be eligible to bear the claim.

The amounts of vitamin D that are allowed in flavored milk and milk drinks (89 IU/100 g) and certain fruit juices and drinks (100 IU/serving) are similar to the amount that is needed to be eligible for the calcium and vitamin D and osteoporosis health claim (at least 80 IU per RACC). The amounts of vitamin D in certain fortified cereals (350 IU/ 100 g) would provide a higher amount of vitamin D. For example, a serving of a ready-to-eat biscuit-type breakfast cereal with a RACC of 55 g (see Table 2 in § 101.12(b)) with the maximum amount of vitamin D added would contain 192 IU of vitamin D/ RACC.

The agency usually assumes that food consumption patterns generally reflect 3 meals a day and a snack, with about 25 percent daily intake for each (58 FR 2303 at 2379; January 6, 1993). Using this approach, considering 4 servings a day from either the lowest (42 IU) or the highest (350 IU) vitamin

D containing categories that could be eligible for a vitamin D and calcium and osteoporosis health claim, one could consume from approximately 170 to 1,400 IU of vitamin D. Thus, consumers who choose foods that bear the calcium and vitamin D and osteoporosis health claim would be able to incorporate such foods into the diet in a manner that would likely keep their total intake of vitamin D well below the UL of 2,000 IU per day. For example, a serving of a biscuit-type cereal with the maximum amount of vitamin D added (192 IU) prepared with 1/2 cup of skim milk, which also has the maximum amount of vitamin D added (51 IU), for breakfast would provide 243 IU of vitamin D. A glass of orange juice with the maximum amount of vitamin D added for lunch and as an afternoon snack would provide 200 IU of vitamin D. At dinner a serving of low-fat yogurt, to which vitamin D has been added as an optional ingredient, would provide 92 IU of vitamin D. The total vitamin D intake from these foods would provide 535 IU of vitamin D in a day. Furthermore, FDA believes it reasonable to consider that consumers who supplement their diets with vitamin D would likely be consuming the most frequent level of vitamin D containing supplements (400 IU) per day. Thus, consumers who choose foods that bear the calcium and vitamin D and osteoporosis health claim and that consume a vitamin D supplement would likely keep their total intake of vitamin D below the UL of 2,000 IU/day. The agency believes it is unlikely that consumers would be consuming total amounts of vitamin D, from both conventional foods and dietary supplements that can bear the claim, at levels that would pose a safety concern.

Therefore, FDA tentatively concludes, that the use of vitamin D in conventional foods, at levels necessary to justify the claim, as described in section IV.A.2 of this document, and in accordance with the GRAS affirmation

(§ 184.1950) or the food additive regulation (§ 172.380), is safe and lawful under the applicable food safety provisions of the act. Further, FDA tentatively concludes that use of vitamin D as a dietary ingredient or dietary supplement, at levels necessary to justify the claim, as described in section IV.A.2 of this document is safe and lawful under the applicable food safety provisions of the act. Thus, FDA tentatively concludes that the preliminary requirements in 21 CFR 101.14(b)(3)(ii) are satisfied.

b. *Calcium*

The petitioner stated the preliminary requirements for a health claim for calcium and osteoporosis, including the requirement that the substance is safe and lawful at the level necessary to justify a claim, have already been established, as evidenced by the currently authorized claim. In the 1993 calcium and osteoporosis health claim final rule, FDA concluded that calcium's use at the levels necessary to justify the claim was safe and lawful under the applicable food safety provisions of the act (58 FR 2665 at 2670). At the time the calcium and osteoporosis health claim was authorized, in order for a food or dietary supplement to carry the claim, it had to meet or exceed the requirements for a "high" level of calcium as defined in § 101.54(c). A "high" level of calcium is at least 20 percent of the RDI of calcium per RACC. The RDI for calcium is 1,000 mg/day. Twenty percent of the RDI for calcium (200 mg) is well below the UL of 2,500 mg for calcium.

In the final rule for the authorized health claim about calcium and osteoporosis (21 CFR 101.72) (58 FR 2665 at 2670), FDA identified 10 specific calcium compounds that are deemed to be safe and lawful for use in a dietary supplement or as a nutrient supplement (i.e., added to food) that may bear the calcium and osteoporosis health claim. The 10 compounds (calcium

carbonate, calcium citrate, calcium glycerophosphate, calcium oxide, calcium pantothenate, calcium phosphate, calcium pyrophosphate, calcium chloride, calcium lactate, and calcium sulfate) are either approved as food additives (21 CFR part 172), GRAS substances (21 CFR part 182), or affirmed as GRAS substances (21 CFR part 184).

At the time FDA published the final rule authorizing the health claim about calcium and osteoporosis (January 6, 1993), ingredients used in dietary supplements were subject to the premarket safety evaluations required for new food ingredients and for new uses of food ingredients. That is, such ingredients were required to be approved as food additives, determined as GRAS substances, or affirmed as GRAS substances before they could be used in food, including dietary supplements. With passage of the Dietary Supplement Health and Education Act in 1994 (DSHEA) (Public Law 103–417), Congress amended the act to provide that ingredients for dietary supplements are exempt from premarket safety evaluations for food additives or GRAS substances. Instead, Congress provided that dietary ingredients are subject to the adulteration provisions in section 402 of the act (excluding the food additive adulteration provision), and, if applicable, the new dietary ingredient provisions in section 413 of the act, which pertain to dietary ingredients that were not marketed in the United States before October 15, 1994. Therefore, the uses of these sources of calcium are subject to review under different provisions of the act, depending upon their use in or as a conventional food, or alternatively, as a dietary ingredient or dietary supplement. Since authorization of the calcium and osteoporosis health claim, no other calcium compound, other than the 10 discussed previously, has been demonstrated to FDA's satisfaction to be safe

and lawful for use in a dietary supplement or as a nutrient supplement in conventional food.

Subsequent to the publication of the final rule authorizing the calcium and osteoporosis health claim, the IOM established a UL for calcium based on life stages, gender, and age in 1997 (Ref. 5). Although calcium is known to be an essential nutrient, it can also cause adverse effects. The IOM noted that the adverse effects of excess calcium intake in humans concern calcium intake from "nutrient supplements" i.e., calcium taken as a dietary supplement, and that the most widely studied and biologically important possible adverse effects of excessive calcium intake are kidney stone formation, the syndrome of hypercalcemia and renal insufficiency (milk alkali syndrome), and the interaction of calcium with the absorption of other essential minerals (Ref. 5). Using milk alkali syndrome as the clinically defined critical endpoint, the IOM identified the lowest-observed-adverse-effect level (LOAEL) of calcium intake in the range of 4,000 to 5,000 mg/day. The IOM established 2,500 mg/day of calcium as the UL for individuals over 12 months old by dividing a LOAEL of 5,000 mg/day by an uncertainty factor of 2 to take into account the relatively high prevalence of renal stones in the U.S. population, which is 12 percent, and potential increased risk of hypercalciuria and depletion of other minerals among susceptible individuals.

The most recent nationally representative data, 1999-2000 NHANES, found the median calcium intake from foods, excluding dietary supplements, to be 735 mg/day for all individuals, excluding nursing infants and children (Ref. 12). Calcium can be obtained from dietary supplement sources as well as food sources.

Calcium is often contained in multiple vitamin and mineral supplement products. Most of these products contain about 100 to 200 mg of calcium per RACC and recommended consumption of the dietary supplement once per day (Ref. 11). Some of these products contain 250 to 500 mg calcium with a recommendation of once per day, and 1 product surveyed contained up to 1,000 mg calcium with a recommended serving of once per day (id.). Calcium is also often contained in products where calcium is the sole ingredient or where calcium and vitamin D are the only ingredients. These types of products generally contain between 500 to 1,000 mg of calcium per RACC (id.). Calcium and vitamin D only products with a RACC of 500 mg of calcium recommend consumption of 1 to 3 servings per day and the recommended calcium intake does not exceed 1,500 mg per day (id.). Calcium and vitamin D only products with a RACC of 600 mg of calcium recommend consumption of 1 or 2 servings per day (id.). Products with a RACC greater than 600 mg of calcium recommend consumption of only 1 serving per day (id.). The daily intake level of calcium suggested in calcium and vitamin D only products is between 300 to 1,500 mg/day. Thus, the range of calcium intake from the various types of calcium containing dietary supplement products generally varies from 100 to 1,500 mg calcium per day, which when added to the median level of calcium intake from food (735 mg/day) is 835 to 2,235 mg calcium. This range includes amounts that are below the UL of 2,500 mg/day for calcium.

FDA also considered the amount of calcium that may be added to food in order for foods to be eligible to bear the claim. Foods that are eligible to bear the calcium or the vitamin D and calcium and osteoporosis health claim must contain at least 200 mg calcium per RACC. To estimate the daily intake of calcium from foods, the agency assumed the same food consumption

patterns as considered for vitamin D, since the foods that provide enough calcium to be eligible for the claim or the proposed additional claim, also contain vitamin D. Thus, four servings of foods eligible to bear the health claim would provide at least 800 mg calcium. Such an amount is well below the UL of 2,500 mg calcium. Thus, consumers who choose foods that bear the calcium, or the calcium and vitamin D, and osteoporosis health claim would be able to incorporate such foods into the diet in a manner that would likely keep their total intake of calcium well below the UL of 2,500 mg per day. Furthermore, consumers who choose conventional foods that bear the calcium or the additional calcium and vitamin D claim and that consume up to 1,500 mg of calcium per day from supplements would also likely keep their total intake of calcium below the UL of 2,500 mg per day.

Therefore, FDA tentatively concludes, under the preliminary requirements of § 101.14(b)(3)(ii), that the use of calcium in foods, including dietary supplements, at levels necessary to justify the health claim (20 percent or more of the RDI for calcium) is safe and lawful under the applicable provisions of the act.

III. Review of Scientific Evidence of the Substance-Disease Relationship

A. Basis for Evaluating the Relationship Between Calcium and Vitamin D and Osteoporosis

1. Background of the Relationship Between Calcium and Osteoporosis

FDA authorized the calcium and osteoporosis health claim in response to NLEA, after conducting a review of the scientific literature on calcium and osteoporosis. The current petitioner is requesting, among other things, that the existing health claim for calcium and osteoporosis (§ 101.72) be amended to allow additional language for calcium and vitamin D and osteoporosis. FDA

conducted its review of the effects of calcium and vitamin D on osteoporosis consistent with how the agency conducted its review for calcium and the osteoporosis health claim. Thus, the agency examined the effects of calcium and vitamin D on direct measures of bone status (i.e. bone mineral density (BMD) and bone mineral content (BMC)).

According to the National Institutes of Health (NIH) Consensus Statement "Osteoporosis, Prevention, Diagnosis, and Therapy" (hereinafter, the 2000 NIH Consensus Statement)," osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture (Ref. 2). Bone strength is dependent upon bone density and bone quality. Bone density is determined by peak bone mass and amount of bone loss (Ref. 2). Bone quality is a function of architecture, turnover, damage accumulation (e.g., micro fractures) and mineralization (Ref. 2). A fracture occurs when a failure-inducing force (e.g., trauma) is applied to osteoporotic bone (Ref. 2). Thus, osteoporosis is a significant risk factor for fractures, which are commonly described as osteoporotic fractures. The most common osteoporotic fractures are in the vertebrae, hip, and wrist-forearm.

The most common measures of overall bone strength are those for bone mass, namely, BMD and BMC. Bone mineral content is the amount of mineral at a particular skeletal site such as the femoral neck, lumbar spine, or total body; whereas BMD is BMC divided by the area of the scanned region (Ref. 5). As in the 1991 review, FDA has identified bone mass (i.e., BMD, BMC) as a surrogate endpoint for osteoporosis. Thus, FDA used bone mass to identify osteoporosis risk reduction for the purpose of evaluating the scientific evidence for a health claim about calcium, vitamin D, and osteoporosis (Ref. 2).

2. Physiological Role of Vitamin D in Maintaining Calcium Homeostasis

In humans and other mammals, vitamin D_3 is photosynthesized in the skin by the actions of solar ultraviolet B (UV–B) radiation followed by isomerization, and is the normal dietary form of vitamin D (Ref. 6). Vitamin D_2 is synthesized from ergosterol, a yeast and plant sterol (Ref. 6). Both vitamin D_2 and vitamin D_3 are used as ingredients in conventional food and as dietary ingredients in dietary supplements. Vitamin D_2 and vitamin D_3 are biologically inert, but serve equally as substrates for the production of the biologically active 1,25-dihydroxy-vitamin D_3 (calcitriol) (Ref. 6). Vitamin D_2 or D_3 is hydroxylated at the 25 position in the liver to produce 25-hydroxy-vitamin D_3 (25-hydroxycholecalciferol), which is then further hydroxylated in the kidney to form 1,25-dihydroxy-vitamin D_3 (Ref. 6).

The predominant biological role of vitamin D is to maintain serum calcium and phosphorus concentrations within their normal ranges (Ref. 6). 1,25-dihydroxy-vitamin D_3 acts directly on intestinal mucosal cells to increase absorption of calcium and on bone to further release calcium (Refs. 6 and 13). If dietary calcium intake is inadequate and serum calcium concentration starts to drop below required levels, the parathyroid produces parathyroid hormone (PTH), which then stimulates increased production of 1,25-dihydroxy-vitamin D_3 in the kidney. Together, PTH and 1,25-dihydroxy-vitamin D_3 mobilize calcium from bone and stimulate calcium reabsorption in the kidney (Refs. 6, 13 and 14). To prevent hypercalcemia, the elevated 1,25-dihydroxy-vitamin D_3 acts as a negative feedback regulator on the parathyroid gland to reduce PTH secretion (Ref. 13). In addition, elevated serum calcium concentrations stimulate thyroid production of calcitonin, which lowers the circulating calcium levels by preventing bone resorption and increasing renal calcium

excretion (Ref. 15). Thus, 1,25-dihydroxy-vitamin D_3 first acts by increasing intestinal calcium absorption and then, if dietary calcium is not adequate and serum calcium concentration remains low, PTH increases 1,25-dihydroxy-vitamin D_3 levels to increase calcium reabsorption from urine and ultimately liberate calcium stores from bone (Ref. 14).

B. Review of the Scientific Evidence of the Substance-Disease Relationship

The petitioner requested, among other things, that the existing health claim for calcium and osteoporosis (§ 101.72) be amended to allow additional language for calcium and vitamin D intake and reduced risk of osteoporosis. The petitioner also requested other amendments, in addition to including calcium and vitamin D as a substance of the claim, and the agency will discuss the scientific evidence about these other proposed amendments in sections IV. B through F of this proposed rule.

FDA has previously concluded that there is significant scientific agreement among qualified experts to support the relationship between calcium intake and reduced risk of osteoporosis (58 FR 2665 at 2672). FDA is not changing this conclusion. There is still significant scientific agreement for such a relationship (Refs. 2, 4, and 16). Since the petitioner has requested that the agency authorize an additional claim for calcium and vitamin D intake and osteoporosis, FDA focused its review on studies that examined the effects of calcium and vitamin D intake on osteoporosis risk. In order to authorize a health claim relating calcium and vitamin D intake to reduced risk of osteoporosis, FDA will consider whether there is significant scientific agreement among qualified experts to support the relationship between calcium and vitamin D intake and reduced risk of osteoporosis. FDA's review of the evidence to support an amendment to include calcium and vitamin D

as a substance of the calcium and osteoporosis health claim was conducted consistent with FDA published guidance on significant scientific agreement in the review of health claims (Ref. 17).

The petition cited 221 references that summarized 3 bodies of evidence in support of the health claim for calcium and vitamin D intake and risk of osteoporosis. These included studies on the relationship between: (1) Calcium intake and risk of osteoporosis, (2) vitamin D intake and risk of osteoporosis, and, (3) calcium and vitamin D intake and risk of osteoporosis. Scientific conclusions about the substance-disease relationship cannot be drawn from studies that did not analyze whether calcium plus vitamin D, together, were associated with risk factors for osteoporosis (BMD or BMC).

1. Assessment of Intervention Studies

FDA identified a total of 13 intervention studies in the petition on calcium and vitamin D intake and risk of osteoporosis for its review of the proposed calcium and vitamin D and osteoporosis health claim (Refs. 18 through 30). Scientific conclusions about the substance-disease relationship could not be drawn from three of these studies. Specifically, Aloia et al. (1994) (Ref. 18) and Prestwood et al. (1999) (Ref. 28) did not include appropriate control groups that would allow assigning any observed effects to calcium and vitamin D supplementation (Ref. 31). Therefore, it could not be determined whether changes in the endpoint of interest were due to calcium or vitamin D intake or to unrelated and uncontrolled extraneous factors (Ref. 31). In addition, Prestwood et al. (1999) measured outcomes (biochemical markers of bone formation and resorption) that are not recognized as valid surrogate endpoints for osteoporosis. The only validated surrogate endpoints for osteoporosis are BMD and BMC. Grados et al. (2003) (Ref. 25) studied women with vitamin

D deficiency and the results could not be extrapolated to the general population. Nutrient status and metabolism can be severely altered when an individual is malnourished. Vitamin D deficiency causes abnormalities in calcium and bone metabolism (Ref. 6). Vitamin D deficiency will cause a decrease in ionized blood calcium, which will lead to an increase in the production of secretion of parathyroid hormone (Ref. 6). The effect of vitamin D on calcium and bone metabolism can be different than the effect of the same nutrient on healthy, well-nourished individuals. Therefore, scientific conclusions cannot be drawn from this study.

Thus, FDA identified 10 reports of 8 intervention studies, which included 2 followup studies (Refs. 21 and 24), from which scientific conclusions could be drawn about the effects of calcium and vitamin D intake on reduced risk of osteoporosis (Refs. 19 through 24 and Refs. 26, 27, 29, and 30).

Orwoll et al. (1990) (Ref. 27) was a 3-year, randomized, double-blind placebo-controlled study that provided U.S. men (n=36 control group; n=41 treatment group; mean of 58 years for both groups) a supplement containing 1,000 mg/day calcium and 1,000 IU/day vitamin D or a placebo. IU is equivalent to the specific biological activity of 0.025 microgram (μg) of vitamin D_3 (i.e., 1 mcg equals 40 IU; 1 milligram (mg) equals 40,000 IU). There was no effect of calcium and vitamin D supplementation on BMC (radius, vertebrae) when compared to men receiving a placebo (Ref. 27).

Chapuy et al. (1992, 1994) reported the results from 1 1/2 years (Ref. 20) and 3 years (Ref. 21) supplementation of French women (n=1,634/group; 84 years mean) with 1,200 mg/day calcium and 800 IU/day vitamin D or a placebo. In this randomized, double-blind placebo-controlled study, calcium and vitamin D supplementation resulted in significantly fewer hip and non-

vertebral osteoporotic fractures (Refs. 20 and 21) and improved proximal femur BMD (Ref. 21), compared with the placebo group.

Dawson-Hughes et al. (1997) (Ref. 23) provided a placebo or a supplement containing 500 mg/day calcium and 700 IU/day vitamin D to U.S. men and women (n=187–202/group; approximately 70 years mean) in a 3-year randomized, double-blind placebo-controlled study. For all subjects, calcium and vitamin D produced a benefit in BMD (femoral neck, spine, total body) and reduced non-vertebral fracture incidence compared with subjects given placebo. When the BMD results for men (n=86) and women (n=101) were analyzed separately, men had significant effects at all three sites; whereas only total body bone loss was significantly reduced in women. Two years following withdrawal of the calcium and vitamin D supplements, BMD returned to levels observed in the placebo group, with the exception of total body BMD in men, which remained significantly higher in men previously given calcium and vitamin D (Ref. 24).

Kreig et al. (1999) (Ref. 26) was a 2-year randomized, controlled study in which French women (n=50-53/group; 84 years mean) were given a supplement containing 1,000 mg/day calcium and 880 IU/day vitamin D or left untreated. Bone density was significantly higher in the supplemented group compared to the untreated group (Ref. 26).

Baeksgaard et al. (1998) (Ref. 19) was a 2-year, randomized, double-blind placebo-controlled study in which Danish women (n=63-69/group; 62.5 years mean) were given a placebo or a supplement containing 1,000 mg/day calcium and 560 IU/day vitamin D. A significant increase in lumbar spine BMD was observed in the supplemented group compared to the placebo group (Ref. 19).

Sosa et al. (2000) (Ref. 29) provided either a supplement containing 1,000 mg/day calcium or 1,000 mg/day calcium and 1,520 IU/day vitamin D to Spanish women (n=28-30/group; 78 years mean) in a 1-year randomized, active controlled study. Calcium and vitamin D supplementation significantly increased femoral neck BMD compared to the calcium only group. No differences between the groups were observed for fracture incidence (Ref. 29).

Dawson-Hughes et al. (1991) (Ref. 22) provided a supplement containing 377 mg/day calcium or 377 mg/day calcium and 400 IU/day vitamin D to U.S. women (n=124-125/group; 61 years mean) for 1 year in a randomized, double-blind active-controlled study. Spine BMD was significantly higher in the women that received calcium and vitamin D compared to women who received calcium alone (Ref. 22).

Jackson et al. (2006) (Ref. 30) provided a supplement containing 1,000 mg/day calcium and 400 IU/day vitamin D_3 to postmenopausal women (n=16,936; 62 years mean) for 7 years who were already enrolled in a Women's Health Initiative (WHI) clinical trial. This was a randomized, double-blind placebo controlled study. Total hip BMD was significantly higher in women who received calcium and vitamin D compared to women in the placebo group. Spine and whole-body BMD were not significantly different between the groups (Ref. 30).

2. Assessment of Observational Studies

The petition identified 8 observational studies on calcium and vitamin D intake, consisting of 1 prospective cohort (Ref. 32), 2 prospective sub-cohorts (Ref. 33 and 34), and 5 cross-sectional studies (Refs. 35 through 39). The eight observational studies either calculated calcium and/or vitamin D intake from estimates of dietary intake and/or dietary supplements.

When calcium or vitamin D intake is calculated from estimates of intake of calcium or vitamin D containing foods or dietary supplements, human and measurement error can occur, affecting the accuracy of the calculation. In observational studies that calculate nutrient intake from conventional foods or dietary supplements, measure of calcium and/or vitamin D intake is based on recorded dietary intake methods, such as food frequency questionnaires, diet recalls, or diet records, in which the type and amount of foods and dietary supplements consumed are estimated. Calcium and vitamin D levels in conventional foods are then estimated using typical calcium and vitamin D concentration values for the food product category, based on a source such as the U.S. Department of Agriculture National Nutrient Database for Standard Reference. A common weakness of observational studies is the limited ability to ascertain the actual food, dietary supplement or nutrient intake for the population studied as a result of poor memory, over-, or underestimation of portion sizes and recall bias (Ref. 40). Thus, it is difficult to ascertain an accurate amount of the nutrient consumed based on reports of dietary intake from conventional foods and dietary supplement use. Furthermore, the bioavailability of calcium from foods can vary due to food processing and cooking procedures that are not indicated in a recorded dietary intake method or not indicated nor available for foods that have an assigned calcium concentration value (Ref. 41).

In addition, conventional foods and multivitamin and multi-ingredient supplements contain not only calcium and vitamin D, but also other nutrients that may be associated with the metabolism of calcium and vitamin D on bone health. Thus, it is not possible to attribute any observed associations to calcium and vitamin D intake alone from conventional foods and/or multivitamin and

multi-ingredient supplements because of the potential confounding effects from the other components contained in the conventional foods and dietary supplements. Because conventional foods and dietary supplements consist of many nutrients and substances, it is difficult to study the nutrient or food components in isolation (Ref. 42). For instance, bone health requires more than just calcium and vitamin D (Refs. 4 to 6). Most notably, phosphorus and magnesium make up more than half of bone mineral density (Refs. 4 and 5). Insufficient levels of magnesium may interfere with the ability to metabolize calcium (Ref. 4).

As discussed previously, when evaluating the relationship between vitamin D and calcium and a reduced risk of osteoporosis, there are inherent problems associated with an observational study design in assessing vitamin D and calcium intake from conventional food and/or dietary supplements and in controlling for the intake of other nutrients that may affect vitamin D and calcium metabolism. Based on the problems associated with the use of an observational study design to assess a relationship between calcium and vitamin D intake and a reduced risk of osteoporosis, none of the eight observational studies provided, nor could they provide, a sufficient assessment of the intake of calcium and vitamin D from foods and/or dietary supplements in order to evaluate such a relationship. In addition, none of the eight observational studies controlled for, nor could they control for, the intake from other components in foods and dietary supplements that are associated with the metabolism of calcium and vitamin D, which control is necessary in order to evaluate the relationship between calcium and vitamin D and a reduced risk of osteoporosis. Further, two of these studies (Refs. 34 and 36) measured serum vitamin D levels, which are not a valid biomarker of dietary vitamin

D intake because serum levels reflect the cumulative effect of both exposure to sunlight and dietary intake (Ref. 6). For the previously stated reasons, FDA concludes that no scientific conclusions about the relationship between calcium and vitamin D intake and the risk of osteoporosis can be drawn from the eight observational studies on conventional foods or dietary supplements.

3. Authoritative Statements

In its review of the scientific evidence, FDA also considered conclusions from the 2000 NIH Consensus Statement, which was submitted with the petition, and the Surgeon General Report "Bone Health and Osteoporosis" (hereafter, the 2004 Surgeon General Report) (Refs. 2 and 4). The 2000 NIH Consensus Statement concluded that "adequate calcium and vitamin D intake are crucial to develop optimal peak bone mass and to preserve bone mass throughout life" and further, "osteoporosis occurs in all populations and at all ages" (Ref. 2). Similarly, the 2004 Surgeon General Report states that "calcium and vitamin D intake and physical activity are now known to be major contributors to bone health for individuals of all ages, and while bone disease often strikes late in life, the importance of beginning prevention at a very young age and continuing it throughout life is now well understood" (Ref. 4). These results extend the scientific conclusions that not only calcium reduces the risk of osteoporosis but that calcium and vitamin D also reduce the risk of osteoporosis.

IV. Decision to Amend the Calcium and Osteoporosis Health Claim

A. Addition of Vitamin D

The majority of the intervention studies FDA evaluated and submitted with the petition established that calcium and vitamin D significantly reduces the risk of osteoporosis (Refs. 18 through 29). One intervention study (Ref. 29),

which compared calcium supplementation to supplementation with calcium and vitamin D showed no difference in fracture incidence but did demonstrate significantly increased femoral neck BMD with calcium and vitamin D. Another study (Ref. 22) showed a significantly higher spine BMD in women with calcium and vitamin D supplementation compared to calcium supplementation alone. Therefore, the two studies (Refs. 22 and 29) that compared supplementation with calcium to calcium and vitamin D suggest that the combination of calcium and vitamin D may enhance the effects of reduction in risk of osteoporosis when compared to calcium alone. The role of vitamin D in enhancing the bioavailability of calcium through increased intestinal absorption of dietary calcium, and increased renal reabsorption of urinary calcium is well established. Based on its review of the publicly available evidence pertaining to calcium, vitamin D, and osteoporosis, FDA tentatively concludes that there is sufficient evidence to amend § 101.72 to include vitamin D so that, in addition to claims for calcium and osteoporosis, additional claims can be made for calcium and vitamin D and osteoporosis. Accordingly, FDA is proposing to amend § 101.72 to authorize an additional health claim for calcium and vitamin D and reduced risk of osteoporosis.

1. Nature of the Food Eligible to Bear the Calcium and Osteoporosis Claim

The agency is not making any changes to the nature of the food, including dietary supplements, labeled with the calcium and osteoporosis health claim (§ 101.72(c)(2)(ii)). Those requirements are that: (1) The food shall meet or exceed the requirements for a "high" level of calcium as defined in § 101.54(b), i.e., the food must contain 20 percent or more of the RDI for calcium per RACC; (2) the calcium content of the product shall be assimilable; (3) dietary supplements shall meet the United States Pharmacopeia (U.S.P.) standards for

disintegration and dissolution applicable to their component calcium salts, except that dietary supplements for which no U.S.P. standards exist shall exhibit appropriate assimilability under the conditions of use stated on the product label; and (4) the food or total daily recommended supplement intake shall not contain more phosphorus than calcium on a weight per weight basis.

2. Nature of the Food Eligible to Bear the Calcium and Vitamin D and Osteoporosis Claim

The general requirements for health claims (21 CFR 101.14(d)(2)(vii)) provide that, if the claim is about the effects of consuming the substance at other than decreased dietary levels, the level of the substance must be sufficiently high and in an appropriate form to justify the claim. If a definition for the use of the term "high" for the substance has been established, the substance must be present at a level that meets the requirements for the use of that term. A "high" claim about the level of a nutrient in a food in relation to the RDI established for that nutrient requires that the food contain 20 percent or more of the RDI per RACC (see § 101.54(b)). The RDI for vitamin D is 400 IU. Thus, a conventional food must contain 20 percent or more of the RDI for vitamin D per RACC (i.e., at least 80 IU) to be eligible for the additional calcium, vitamin D and osteoporosis health claim. A dietary supplement must contain 20 percent or more of the RDI for vitamin D per RACC (see Table 2 of § 101.12(b)).

Accordingly, FDA is proposing that, in order for a food to be eligible for the additional calcium and vitamin D and osteoporosis health clam the food must: (1) Be eligible to bear a claim for the calcium and osteoporosis health claim in § 101.72, (2) meet or exceed the requirements for a "high" level of

vitamin D as defined in § 101.54(b), and (3) meet all of the general health claim requirements set forth in § 101.14.

B. Amendments to the Calcium and Osteoporosis Health Claim Other Than the Inclusion of Vitamin D

As noted in the section I of this proposed rule, FDA published a proposed rule entitled "Food Labeling: Nutrient Content Claims, General Principles; Health Claims, General Requirements and Other Specific Requirements for Individual Health Claims" (the 1995 proposal), to amend several provisions of the regulations on nutrient content claims and health claims to increase the flexibility in the use of nutrient content claims and health claims on food products (60 FR 66206). The agency either extended or reopened the comment period four times for the 1995 proposal, in response to request from stakeholders (61 FR 11793, March 22, 1996; 62 FR 3635, January 24, 1997; 62 FR 11129, March 11, 1997; and 69 FR 24541, May 4, 2004). The agency received approximately 160 comments in response to the proposed rule. The comments specific to the requirements for the calcium and osteoporosis health claim generally supported the agency's tentative proposals. Specific comments are discussed below as they pertain to the appropriate sections.

C. Elimination of the Requirement to List Race, Age and Sex as Risk Factors for the Development of Osteoporosis

1. The 1995 Proposal

In the 1995 proposal, FDA proposed to amend several specific requirements to the nature of the claim for the calcium and osteoporosis health claim (60 FR 66206). The first required element for the calcium and osteoporosis health claim is contained in § 101.72(c)(2)(i)(A) and provides that:

"The claim makes clear that adequate calcium intake throughout life is not the only recognized risk factor in this multifactorial bone disease by listing specific factors, including sex, race, and age that place persons at risk of developing osteoporosis and stating that an adequate level of exercise and a healthful diet are also needed." The original intent of presenting the information as specified in § 101.72(c)(2)(i)(A) was to convey the message that for any individual several factors define disease risk.

FDA's tentative decision to amend § 101.72(c)(2)(i)(A) in the 1995 proposal was based, in part, on the 1994 NIH Consensus Statement on optimal calcium intake, which was published after authorization of the calcium and osteoporosis final rule. The first of several significant conclusions from the 1994 NIH Consensus Statement was that a large percentage of Americans did not meet the currently recommended guidelines for optimal calcium intake (Ref. 43). Because of the need to correct this public shortfall and to improve bone health, which would reduce the risk of osteoporosis, FDA tentatively concluded that a singular focus on achieving and maintaining adequate calcium intake as a required element of the claim was important (60 FR 66206 at 66216). In the 1995 proposal, FDA also acknowledged, that the number of food products bearing health claims, during this time, was not as great as the agency had anticipated and FDA was concerned that manufacturers may have been disinclined to use such lengthy health claims on food labels. (id.) These concerns coupled with the fact that most Americans, regardless of sex, race, or age, were not meeting the recommended guidelines for optimal calcium intake led the agency to reevaluate the requirement in § 101.72(c)(2)(i)(A). Accordingly, FDA proposed to simplify § 101.72(c)(2)(i)(A) by limiting the requirement to a balanced statement that reflects the importance of the nutrient

calcium over a lifetime in a healthful diet to reduce osteoporosis risk, but that does not imply that calcium is the only risk factor for the development of osteoporosis. FDA also proposed to replace the provision in § 101.72(c)(2)(i)(A) that the specific risk factors and the need for an adequate level of exercise be stated in the claim, with the more simple requirement that the claim not imply that adequate dietary calcium intake is the only recognized risk factor for a reduced risk of osteoporosis (60 FR 66206 at 66216 and 66217). In concert with these proposed changes to § 101.72(c)(2)(i)(A), FDA provided that the claim may list the sex, age, or race of populations at risk for osteoporosis, or the need for an adequate level of exercise as optional information (60 FR 66206 at 66217).

The agency did not receive any comments opposing these proposed amendments. Rather, several comments that addressed this issue supported the agency's tentative amendments to § 101.72(c)(2)(i)(A). The agency considered these comments when responding to the health claim petition submitted by The Beverage Institute for Health and Wellness.

2. The Beverage Institute for Health and Wellness Petition

The petitioner requested that the agency amend § 101.72(c)(2)(i)(A) to eliminate reference to age, sex, race, and the need for an adequate level of exercise. The petitioner did not include the provision in § 101.72(c)(2)(i)(A) concerning calcium's role in a 'healthful diet' and did not state why such provision was not included in their proposed amendment. The petitioner stated that their request for eliminating reference to age, sex, and race in the claim was supported by scientific evidence establishing that calcium or calcium and vitamin D reduces the risk of osteoporosis in all age groups of both sexes and in all races. The petitioner stated that their request for

eliminating reference to the need for an adequate level of exercise from the claim was supported by scientific evidence, submitted with the petition, showing that calcium or calcium and vitamin D can reduce the risk osteoporosis regardless of the level of physical activity.

3. Agency's Proposed Amendments to the Calcium and Osteoporosis Health Claim

The agency agrees with the petitioner that the claim no longer needs to list specific risk factors for the development of osteoporosis, including sex, race, and age. However, the agency also tentatively concludes that a reference to a "healthful diet" and to adequate physical activity is still a necessary part of the claim, as well as the importance of adequate calcium or adequate calcium and vitamin D intake throughout life.

Sex, Age, and Race Categories

The 2000 NIH Consensus Statement concluded that "osteoporosis occurs in all populations and at all ages" and that "adequate calcium and vitamin D intake are crucial to develop optimal peak bone mass and to preserve bone mass throughout life" (Ref. 2). Furthermore, evidence provided in the 2004 Surgeon General's Report as well as the 2000 NIH Consensus Statement establishes that the benefits of calcium or calcium and vitamin D on prevention of bone diseases, including osteoporosis, are not dependent on age and not specific to any subpopulation in the United States (Refs. 2 and 4).

Osteoporosis occurs in all populations at all ages (Ref. 4). Osteoporosis is the major cause of fractures in the elderly, both men and women. It begins later in men than women (Ref. 2). In women it often follows menopause, especially in white women. Osteoporosis is a disease that takes many years to develop and most often is not discovered until the later years. For every

10 white women, 4 by age 50 or older in the United States will experience a hip, spine, or wrist fracture sometime during the remainder of their lives and for white men the number is 13 percent (Ref. 44). Though the lifetime risk for types of fractures is less in men and nonwhite women, it does represent a significant risk and may be increasing in certain populations, such as Hispanic women (Ref. 45). Because of the mistaken view that osteoporosis is a disease that affects postmenopausal white women, it often goes undetected in men and racial and ethnic minorities (Ref. 4). Risk of developing osteoporosis is likely to increase for all ethnic groups as people's lifespan increases (Ref. 4).

Achieving and maintaining optimal bone health is a process that occurs in both men and women throughout the lifespan (Ref. 2). Bone mineral density declines with age in both men and women. Peak bone mass is achieved at an early age and is a life-long determinant of skeletal health. Calcium is the most important nutrient for achieving and maintaining good skeletal health and vitamin D is required for optimal absorption and utilization of calcium (Refs. 2 and 4). Thus, specific reference to sex, race, and age is not necessary since the benefits of dietary intake of calcium, or calcium and vitamin D would apply to both sexes and all age and race categories.

Healthful Diet

Studies have shown that a well-balanced diet is important for bone health throughout life (Ref. 4). Calcium and vitamin D remain the primary nutrients required for good bone health and consuming diets that include foods that contain these nutrients is critical. In addition, other nutrients such as vitamin K, vitamin C, copper, manganese, zinc, potassium, iron, and others may also play a role in optimal bone health (Ref. 4). Thus, since many nutrients are

involved in bone health, it is important to consume a well-balanced diet that consists of a variety of foods, including grains, fruits, vegetables, nonfat or low-fat dairy products or other calcium-rich foods, meat or beans.

In the 1995 proposal, FDA stated that it included a reference to a "healthful diet" in § 101.72(c)(2)(i)(A) for consistency with the general requirement in § 101.14(d)(2)(v) that "the claim enable the public ***to understand the relative significance of such information in the context of a total daily diet" (60 FR 66206 at 66216). Similar to what the agency concluded in the 1995 proposed rule for the effect of adequate calcium intake, the effect of calcium and vitamin D can only be realized if the calcium and vitamin D is a part of a healthy, well-balanced diet that provides all essential and other nutrients to optimize nutritional health status. Thus, the agency is retaining the requirement in § 101.72(c)(2)(i)(A) that the claim make clear the importance of adequate calcium intake, or when appropriate, adequate calcium and vitamin D intake over a lifetime in a healthful diet is essential to reduce osteoporosis risk.

Physical Activity

Physical activity, along with intake of calcium and vitamin D, is known to be a major contributor to bone health for people of all ages (Ref. 4). In order to reduce the risk of osteoporosis, it is important to begin physical activity at an early age and continue throughout life. Physical activity needs to be maintained for optimal bone health. Physical activity helps to increase or preserve bone mass and reduces the risk of falls (Ref. 4). Studies have shown that physical activity, as well as diet, are responsible for 10 to 50 percent of bone mass and structure (Ref. 4). Physical activity plays an important role in

skeletal health. Thus, physical activity has a significant impact on one's risk for developing osteoporosis.

Two studies have shown that physical activity can have a more beneficial effect in infants or young children if these groups have adequate calcium intakes (Refs. 46 and 47). As with children, the positive effects of physical activity and calcium in older adults on bone health has also been shown (Ref. 4). Thus, there is a synergistic effect between intake of calcium and physical activity.

Both the more current 2004 Surgeon General's Report (Ref. 4), and the 2000 NIH Consensus Statement continue to emphasize the importance of physical activity on bone health (Ref. 2). Thus, because physical activity is integral to bone health, along with the need for adequate calcium, and, as applicable, calcium and vitamin D, the agency is requiring a reference to the need for physical activity as part of the health claim.

In summary, FDA tentatively concludes that specific reference to sex, race, age in the claim is no longer necessary since the benefits of calcium or calcium and vitamin D apply to both sexes at all ages and race categories. FDA also tentatively concludes, however, that the nutritional status of the diet and physical activity have a significant impact on bone health, and thus, one's risk of developing osteoporosis. Accordingly, FDA, is proposing to eliminate the provision in § 101.72(c)(2)(i)(A) that specific risk factors including sex, race, and age be listed in the claim, but to retain the provisions concerning a healthful diet and exercise. Thus, the proposed revision to § 101.72(c)(2)(i)(A) reads as follows: "The claim makes clear the importance of adequate calcium intake or when appropriate, adequate calcium and vitamin D intake throughout life, in a healthful diet along with physical activity are essential to reduce

osteoporosis risk. The claim does not imply that adequate calcium intake or when appropriate, adequate calcium and vitamin D intake is the only recognized risk factor for the development of osteoporosis."

FDA is requesting comments on whether the provision to specify sex, race, or age in the claim language should be retained and why.

D. Elimination of the Requirement that the Claim Not State or Imply that the Risk of Osteoporosis is Equally Applicable to the General Population, and that the Claim Identify the Populations at Particular Risk for the Development of Osteoporosis

1. The 1995 Proposal

The second element for the calcium and osteoporosis claim is contained in § 101.72(c)(i)(2)(B) and provides that: "The claim does state or imply that the risk of osteoporosis is equally applicable to the general United States population. The claim shall identify the populations at particular risk for the development of osteoporosis. These populations include White (or the term ("Caucasian") women and Asian women in their bone forming years (approximately 11 to 35 years of age or the phase "during teen or early adult years" may be used). The claim may also identify menopausal (or the term "Middle-aged") women, persons with a family history of the disease, and elderly (or "older") men and women as being at risk."

FDA's tentative decision to amend § 101.72(c)(2)(i)(B) in the 1995 proposed rule was based on the 1994 NIH Consensus Statement and an FDA report published in 1995 on consumer understanding of health claims (hereinafter referred to as the 1995 FDA health claims report (Ref. 48)).

The 1994 NIH Consensus Statement concluded that the two most important factors that influence the occurrence of osteoporosis are optimal

bone mass attained in the first two or three decades of life and the rate at which bone loss occurs in later years (Ref. 43). Thus, the 1994 NIH Consensus Statement did not ascribe the relative risk of osteoporosis on the basis of race or ethnicity.

As part of the 1995 FDA health claims report, FDA tested participants understanding of a model calcium and osteoporosis health claim, such as the following: "Regular exercise and a healthy diet with enough calcium helps teen and young adult white and Asian women maintain good bone health and may reduce their high risk of osteoporosis later in life."

Results from this study (Ref. 48) showed that minority women were unanimous in objecting to the inference that black American women do not need calcium and questioned the accuracy of the information contained in the claim. All of the survey participants recognized that calcium is essential for everyone. Although there was some recognition based on prior knowledge that younger women need to be concerned about osteoporosis, no participant thought the model claim communicated that concept very well.

The agency did not intend that the calcium and osteoporosis health claim imply that calcium is not needed by any individual or specific population. Given that calcium is essential for every person, the agency attempted to present this disease claim in a truthful, nonmisleading, and scientifically valid manner. Likewise, the agency tentatively concluded in the 1995 proposal that greater use in food labeling of the calcium and osteoporosis health claim, articulated in a manner that will be accepted and followed by consumers, could help support significant strides in improving calcium intake in all segments of the U.S. population. Thus, the agency proposed to revise § 101.72(c)(2)(i)(B) by removing the provision that the claim identify by race

and ethnicity those populations at particular risk for the development of osteoporosis, but to retain identification of teen and young adult women, irrespective of race as the focus of the claim (60 FR 66206 at 66218).

All comments received from the 1995 proposal regarding identification of the at-risk population by race and ethnicity agreed with FDA's tentative decision to remove that requirement from § 101.72(c)(2)(i)(B). However, most of the same comments disagreed with the tentative decision to retain a focus on teen and young adult women. One comment stated that, if the agency were to rely on the 1994 NIH Consensus Statement (Ref. 43) in making its decision, the health claim would also have to cite older people as a second group for whom calcium intake is important, which would lengthen the claim sufficiently to discourage its use on food labels. It said that requiring the claim to emphasize the calcium needs of young adults and teenagers might lead other consumers to conclude that calcium is not important for them. The comment stated that nearly all teens and adults will need encouragement to reach the high levels of calcium, 1,000 to 1,500 mg per day, recommended by the 1994 NIH Consensus Statement. Several comments urged the agency to allow calcium and osteoporosis claims to express the lifelong need for adequate dietary calcium without requiring the identification of any particular population segment as being at a higher than average risk for the disease. The comments stated that a claim such as "adequate calcium in a healthful diet throughout life may reduce the risk of osteoporosis" would be appropriate. The agency considered these comments when responding to the health claim petition submitted by The Beverage Institute for Health and Wellness.

2. The Beverage Institute for Health and Wellness Petition

The petitioner included, in proposed language for § 101.72(c)(2)(i)(B), that the claim not state or imply that the risk of osteoporosis is equally applicable to the general U.S. population. In addition, the petition included, as optional, a statement that identifies other populations at risk for developing osteoporosis, including women in their bone forming years from approximately 11 to 35 years of age. The petitioner provided scientific evidence that calcium and calcium and vitamin D reduce the risk of osteoporosis in both men and women in all age groups regardless of race or ethnicity.

3. Agency's Proposed Amendments to the Calcium and Osteoporosis Health Claim

Scientific evidence from both the Surgeon General's Report on Bone Health and Osteoporosis and the 2000 NIH Consensus Statement shows that osteoporosis occurs in both sexes at all ages and that adequate calcium and vitamin D are essential to the development of peak bone mass and the preservation of bone mass throughout life (Refs. 2 and 4).

Osteoporosis does not affect everyone to the same degree (Ref. 4). Osteoporosis is most prevalent in postmenopausal women (Ref. 4), and white postmenopausal women experience almost 75 percent of hip fractures and have the highest age adjusted fracture incidence (Ref. 2). Both men and women experience an age-related decline in BMD starting in midlife, and men, especially older men do develop osteoporosis (Ref. 4).

Based on the Surgeon General's Report on Bone Health and Osteoporosis and the 2000 NIH Consensus Statement, specifically that osteoporosis is most prevalent in White postmenopausal women (Refs. 2 and 4), FDA tentatively concludes that the provision in § 101.72(c)(2)(i)(B) that the claim must identify

certain populations for particular risk for osteoporosis as White or Asian women between the ages of 11 and 35 is no longer correct.

FDA also tentatively concludes that the provision in § 101.72(c)(2)(i)(B) providing that the claim not state or imply that the risk of osteoporosis is equally applicable to the general population is no longer appropriate. While the risk of osteoporosis is not equally applicable to the general population, in the sense that there may be some subpopulations that are at a greater risk for developing osteoporosis than others, osteoporosis still occurs in all populations at all ages (Refs. 2 and 4). Since osteoporosis is most prevalent and thus more associated with White postmenopausal women, it often has gone unrecognized in men and other age and ethnic populations (Refs. 2 and 4). Thus, FDA tentatively concludes that it is no longer necessary to limit the wording of the claim to targeted subgroups, even though such subgroups may be at a relatively greater risk than others in the general population. Accordingly, FDA is proposing to eliminate the requirement in § 101.72(c)(2)(i)(B).

FDA is requesting comments about whether the identification of any population or populations at particular risk of osteoporosis should be required or optional in the claim language and why.

E. Elimination of the Requirement that the Claim Identify the Mechanism by Which Calcium Reduces the Risk of Osteoporosis

1. The 1995 Proposal

Section 101.72(c)(2)(i)(C) of the calcium and osteoporosis health claim established a requirement for identifying the mechanism whereby adequate dietary calcium over a lifetime reduces the risk of osteoporosis as described below: "The claim states that adequate calcium intake throughout life is linked

to reduced risk of osteoporosis through the mechanism of optimizing peak bone mass during adolescence and early adulthood. The phrase "build and maintain good bone health" may be used to convey the concept of optimizing peak bone mass. When reference is made to persons with a family history of the disease, menopausal women, and elderly men and women, the claim may also state that adequate calcium intake is linked to reduced risk of osteoporosis through the mechanism of slowing the rate of bone loss." The agency concluded in developing this requirement, for the calcium and osteoporosis health claim, that it was important for consumers to have a basic understanding of the biological and physiological mechanisms by which adequate dietary intake of calcium achieves a reduced risk of osteoporosis (60 FR 66206 at 66218).

In the 1995 proposal, FDA proposed to make the statement of the mechanism by which calcium intake affects the risk of osteoporosis optional information (60 FR 66206 at 66218). This tentative conclusion was based on information contained in the 1995 FDA health claims report, which focused on consumer understanding of health claims (Ref. 48). The 1995 FDA health claims report found that because participants had learned elsewhere that calcium intake is related to general bone health, they thought the food label was not the right means for conveying this information. The awareness by consumers that calcium's ability to "build and maintain good bone health" is the mechanism whereby risk of osteoporosis is reduced raised the question as to whether there was a need to state that fact in a health claim. Thus, in the interest of streamlining the claim, FDA proposed to make the statement of the mechanism by which calcium intake affects the risk of osteoporosis

optional information (60 FR 66206 at 66218). No comments were received objecting to this aspect of the 1995 proposal.

2. The Beverage Institute for Health and Wellness Petition

The petitioner requested that the agency allow information on the mechanism by which calcium reduces the risk of osteoporosis to be optional instead of required, and to extend this optional information to the additional calcium and vitamin D and osteoporosis claim.

3. Agency's Proposed Amendments to the Calcium and Osteoporosis Health Claim

Based on the petitioner's request and FDA's tentative conclusions in the 1995 proposal that many consumers were aware that calcium was necessary for good bone health, FDA is proposing to eliminate the requirement in § 101.72(c)(2)(i)(C) that the claim state the mechanism by which calcium reduces osteoporosis risk. FDA is also proposing that information of the mechanism by which calcium reduces the risk of osteoporosis may be optional, for either the calcium or the newly proposed calcium and vitamin D and osteoporosis claim. FDA requests comments on the proposed amendments to § 101.72(c)(2)(i)(C).

F. Elimination of the Requirement in § 101.72(c)(2)(i)(E) that Certain Products Bearing the Claim Include a Statement that Reflects the Limits on the Benefits from Calcium

1. The 1995 Proposal

Section 101.72(c)(2)(i)(E) contains a conditional requirement that a calcium and osteoporosis health claim include a statement that reflects the limit on the benefit derived from dietary calcium intake when the food

contains 40 percent or more of the RDI of 1,000 mg of calcium per day or 400 mg or more of calcium per RACC as defined in § 101.12(b).

In the 1995 proposal, FDA proposed to amend this requirement by increasing the amount of calcium present in a food that would trigger the conditional requirement in § 101.72(c)(2)(i)(E), from 400 mg per RACC to 1,500 mg per day (60 FR 66206 at 66219). FDA based this proposal on conclusions from the NIH 1994 Consensus Statement regarding methods to achieve optimal calcium intake and the absence of reported adverse effects with moderate supplementation up to 1500 mg/day (60 FR 66206 at 66219). FDA's proposal to increase the threshold level in § 101.72(c)(2)(i)(E) was also based on several Congressional findings in the Dietary Supplement Health and Education Act of 1994 (Public Law 103–417) (60 FR 66206 at 66218). One of those findings identified a link between ingestion of certain nutrients or dietary supplements and reduced risk of several chronic diseases, including osteoporosis, and stated that the Federal government should not take any actions to impose unreasonable regulatory barriers that limit or slow the flow of safe products and accurate information to consumers.

One comment did not support FDA's tentative decision to amend § 101.72(c)(2)(i)(E) to change the threshold from 400 mg of calcium per RACC to 1,500 mg per day. The comment stated that a statement that reflects the limit on the benefit derived from dietary calcium intake is needed to protect consumers from over consumption of this nutrient. The comment stated that 400 mg of calcium per RACC should be retained as the threshold since most calcium-rich conventional foods do not contain more than that amount and would not have to bear this type of statement as part of a calcium and osteoporosis health claim. The comment maintained that this approach is

appropriate because such a statement on conventional foods would appear to run at cross purposes with the goal to increase calcium consumption and would be inconsistent with the conclusion in the 1994 NIH consensus statement that "the preferred source of calcium is through calcium-rich foods such as dairy products."

The comment maintained that, because calcium supplements provide calcium in addition to the calcium that consumers get from conventional foods, it is important for consumers to know the maximum recommended safe dose, and cited a second conclusion from the 1994 NIH consensus statement that "practices that might encourage total calcium intake to approach or exceed 2,000 mg per day seem more likely to produce adverse effects and should be monitored carefully." The comment suggested that consumers should be made aware that a total daily intake of 2,000 mg of calcium from conventional foods and dietary supplements appears to be safe, but that higher intakes provide no further benefit. The comment maintained that a lower threshold for a statement of the limits of benefit on calcium supplements would not limit the flow of these supplements to those who need them but would provide information to help prevent their overuse by consumers.

The comment stated further that if FDA did raise the 400 mg calcium per RACC threshold, several issues should be addressed. The comment stated that FDA's proposal to require that the statement of limited benefit apply to foods that provide more than 1,500 mg of calcium per day means that the requirement pertains only to supplements and not to foods since, for conventional foods, the requirement must be on a per reference amount basis. The comment stated that the per day basis could only apply to supplements.

Noting that the highest recommendation for calcium intake in the 1994 NIH consensus statement was 1,500 mg calcium per day, the comment maintained that this level represents total dietary calcium intake from conventional foods and dietary supplements. The comment stated that 1,500 mg should not be the threshold level for a limited benefit statement. The comment argued that setting the threshold higher than 1,000 mg per day would encourage supplementation to an inappropriately high level. The comment pointed out that the Food and Nutrition Board's text, "Eat for Life," advises consumers to avoid taking vitamin or mineral dietary supplements in excess of the U.S. Recommended Dietary Allowance (currently, the Reference Dietary Intake) in any one day—for calcium, that amount is 1,000 mg per day. Accordingly, the comment recommended that the requirement for the limited benefit statement apply only to dietary supplements of calcium whose recommended total daily intake is 1,000 mg or more per day. The agency considered these comments when responding to the health claim petition submitted by The Beverage Institute for Health and Wellness.

2. The Beverage Institute for Health and Wellness Petition

The petitioner proposed to adopt the amendments to § 101.72(c)(2)(i)(E) exactly as proposed in the 1995 proposal. The petitioner also requested that FDA not extend a conditional requirement for vitamin D in the proposed additional health claim for calcium and vitamin D and osteoporosis.

3. Agency's Proposed Amendments to the Calcium and Osteoporosis Health Claim

FDA has been persuaded to reevaluate the conditional requirement in § 101.72(c)(2)(i)(E) due to the Dietary Reference Intakes (DRIs) established for calcium by the IOM (Ref. 5). DRIs for calcium were established after FDA

proposed amendments to the calcium and osteoporosis health claim in the 1995 proposal and after FDA's receipt of the comment opposing FDA's proposed changes to the conditional requirement in § 101.72(c)(2)(i)(E).

In 1997 the IOM conducted a major review of bone-related nutrients (Ref. 4). A goal of the DRI effort was to determine the level of nutrient intake for normal, healthy individuals that would prevent the development of a chronic condition associated with that nutrient (Ref. 5). The DRIs for calcium, which were based on life stages and gender, were set at intake levels of calcium to achieve adequate calcium balance in the body (i.e., AI) and intake levels of calcium that pose no risk of adverse health effects (i.e., UL). The AI for infants up to 6 months of age is 210 mg/day, for infants ages 7 months through 12 months it is 270 mg/day, for children ages 1 through 3 it is 500 mg/day, for children ages 4 through 8 years it is 800 mg/day, for young adults ages 9 through 18 it is 1,300 mg/day, for individuals aged 19 through 50 it is 1,000 mg/day, for individuals ages 51 and above it is 1,200 mg/day, for pregnant and lactating women ages 14 through 18 it is 1,300 mg/day, and for pregnant and lactating women aged 19 and older it is 1,000 mg/day. The UL for all individuals ages 1 and above is 2,500 mg/day (Ref. 5).

The concept of a threshold level of calcium beyond which no further bone benefit occurs is not presented in either the 2004 Surgeon General's Report or the 2000 NIH Consensus Statement (Refs. 2 and 4). Instead these reports discuss the level of calcium at which calcium poses no risk of adverse health effects (i.e., UL).

When the calcium and osteoporosis health claim was initially proposed the scientific evidence supported the concept that a threshold nutrient intake level existed for calcium, below which bone health was jeopardized, and above

which no further benefit to bone health occurred (56 FR 60689 at 60692 and 60695). Based on two observational studies that reflected findings that calcium intakes of 800 to 1,000 mg of calcium a day appear to be the upper level of calcium intake beyond which no benefit to bone status has been observed and the observation that higher amounts of calcium are needed in old age, FDA proposed to require that a calcium and osteoporosis claim state that a total dietary intake of calcium greater than 200 percent of the RDI has no known additional benefit (56 FR 60689 at 60698). At the time of the 1991 proposal, the proposed RDI for calcium was 950 mg; 200 percent of the RDI was 1,800 mg.

The agency's current thinking is that a statement reflecting the limit on the benefit derived from dietary calcium intake, as derived in the 1991 proposed rule, is no longer the appropriate approach.

Thus, FDA has tentatively concluded not to require a statement about no known further benefit for foods containing 40 percent or more of the RDI of 1,000 mg or 400 mg calcium per RACC. Accordingly, FDA is proposing to eliminate the requirement in § 101.72(c)(2)(i)(E). The agency requests comments on the proposed amendment to eliminate the requirement in § 101.72(c)(2)(i)(E).

V. Description of Modifications to § 101.72

A. Title of the Regulation

FDA is proposing to revise the title of the regulation to: "Health claims: calcium, vitamin D, and osteoporosis." This proposed amendment is necessary to reflect the additional claim for calcium and vitamin D and osteoporosis.

B. General Requirements

1. General requirements

Current § 101.72(a) is entitled "Relationship between calcium and osteoporosis." FDA is proposing to revise § 101.72 to permit additional claims for calcium and vitamin D and osteoporosis. Thus, proposed § 101.72(a) includes information describing the effects of vitamin D on calcium in reducing the risk of osteoporosis, including the scientific evidence that establishes the role of vitamin D in enhancing the effects of calcium in terms of bone health. As a result, FDA is proposing to revise the title for § 101.72(a) to "Relationship between calcium, vitamin D, and osteoporosis."

Current § 101.72(b) sets out the significance of calcium on osteoporosis, describes the various factors that play a role in the development of osteoporosis, a multifactorial bone disease, and stipulates that adequate calcium intake is not the only recognized risk factor for osteoporosis. Since FDA is proposing to amend § 101.72 so that additional claims can be made for calcium and vitamin D and osteoporosis, § 101.72 (b) will need to address the significance of calcium as well as the significance of calcium and vitamin D on osteoporosis. Therefore, FDA is proposing to: (1) Revise the title of § 101.72(b) to "Significance of calcium or calcium and vitamin D" and (2) make it clear that adequate calcium intake or adequate calcium and vitamin D intake are not the only recognized risk factors in the development of osteoporosis.

Current § 101.72(b)(1) sets out key factors of heredity and being female for identifying those individuals most at risk for developing osteoporosis, and includes information on peak bone mass for Caucasian, Asian women, and American women of African heritage. FDA is proposing to remove § 101.72(b)(1).

Current § 101.72(b)(2) discusses the importance of maintenance of an adequate intake of calcium throughout life for the target subpopulation of adolescent and young adult Caucasian and Asian women. If FDA eliminates, as proposed, the requirement that the claim identify adolescent and young adult Caucasian and Asian women between the ages of 11 and 35, as the populations at particular risk for the development of osteoporosis, § 101.72(b)(2) would no longer be appropriate. Therefore, FDA is proposing to update the information in § 101.72(b)(2) and include it in proposed § 101.72(b). Thus, proposed § 101.72(b) will include information about the importance of maintenance of adequate calcium or adequate calcium and vitamin D throughout life and will read as follows: "*Significance of calcium or calcium and vitamin D.* Adequate calcium intake, or adequate calcium and vitamin D intake, is not the only recognized risk factor in the development of osteoporosis, which is a multifactorial bone disease. Maintenance of adequate calcium and vitamin D intakes throughout life is necessary to achieve optimal peak bone mass and to reduce the risk of osteoporosis in later life. However, vitamin D is most effective in this regard when calcium intakes are adequate. Increasing intake of calcium has been shown to have beneficial effects on bone health independent of dietary vitamin D."

2. Requirements on the Nature of the Claim

Section 101.72(c)(2)(i) contains requirements for the nature of the claim. FDA is proposing to revise § 101.72(c)(2)(i) to read as follows: "*Nature of the claim.* A health claim associating calcium, or when appropriate, calcium and vitamin D, with a reduced risk of osteoporosis may be made on the label or labeling of a food described in paragraphs (c)(2)(ii) and (d)(1) of this section, provided that:"

Current § 101.72(c)(2)(i)(A) contains the specific requirement that the claim makes clear that adequate calcium intake throughout life is not the only recognized risk factor in this multifactorial bone disease by listing specific factors, including sex, race, and age that place persons at risk of developing osteoporosis and stating that an adequate level of exercise and a healthful diet are also needed. The agency is proposing to revise § 101.72(c)(2)(i)(A) to read as follows: "The claim makes clear the importance of adequate calcium intake, or when appropriate, adequate calcium and vitamin D intake, throughout life, in a healthful diet along with physical activity, are essential to reduce osteoporosis risk. The claim does not imply that adequate calcium intake, or when appropriate, adequate calcium and vitamin D intake, is the only recognized risk factor for the development of osteoporosis;"

Current § 101.72(c)(2)(i)(B) contains the specific requirement that the claim does not state or imply that the risk of osteoporosis is equally applicable to the general U.S. population. Furthermore, the claim shall identify the populations at particular risk for the development of osteoporosis. These populations include white (or the term "Caucasian") women and Asian women in their bone forming years (approximately 11 to 35 years of age or the phrase "during teen or early adult years" may be used). The claim may also identify menopausal (or the term "middle-aged") women, persons with a family history of the disease, and elderly (or "older") men and women as being at risk. The agency is proposing to remove these specific requirements in § 101.72(c)(2)(i)(B).

Current § 101.72(c)(2)(i)(C) contains the specific requirement that the claim identify the mechanism by which calcium reduces the risk of osteoporosis. The agency is proposing to eliminate this specific requirement and is providing

in new § 101.72(d)(4) that information about the mechanism by which calcium, or when appropriate, calcium and vitamin D, reduces the risk of osteoporosis is optional.

Current § 101.72(c)(2)(i)(D) contains the specific requirement that the claim does not attribute any degree of reduction in risk of osteoporosis to maintaining an adequate calcium intake throughout life. The agency is proposing to revise this specific requirement to include information about calcium and vitamin D. Since the agency is proposing to remove the specific requirements in § 101.72(c)(2)(i)(B) and (c)(2)(i)(C), the agency will redesignate newly revised § 101.72(c)(2)(i)(D) as § 101.72 (c)(2)(i)(B). Thus, § 101.72(c)(2)(i)(B) will read as follows: "The claim does not attribute any degree of reduction in risk of osteoporosis to maintaining an adequate dietary calcium intake, or when appropriate, an adequate dietary calcium and vitamin D intake, throughout life."

Current § 101.72(c)(2)(i)(E) contains the specific requirement that a calcium and osteoporosis health claim include a statement that reflects the limit on the benefit derived from a total dietary calcium intake of greater than 200 percent of the recommended daily intake of calcium (2,000 mg of calcium). The agency is proposing to remove this specific requirement.

Current § 101.72(d)(1) and (d)(2) set out the optional information that may be included in the claim. FDA is proposing to add a new paragraph (d)(1) to include as optional the term "vitamin D" if the food meets or exceeds the requirements for a "high" level of vitamin D as defined in § 101.54(b). Thus, proposed § 101.72(d)(1) will read as follows: " *Optional information.* The claim may include the term "vitamin D" if the food meets or exceeds the requirements for a "high" level of vitamin D as defined in § 101.54(b);"

Since FDA is proposing to add new paragraph (d)(1) to § 101.72, the agency is proposing to redesignate current § 101.72(d)(1) and (d)(2) as § 101.72(d)(2) and (d)(3), respectively. The agency is also proposing to revise newly redesignated § 101.72(d)(3) by removing reference to the publication "Dietary Guidelines for Americans." FDA is proposing to take this action since the "Dietary Guidelines for Americans," may not necessarily contain information on the number of people in the United States who have osteoporosis. Thus, proposed § 101.72(d)(3) will read as follows: "The claim may include information on the number of people in the United States who have osteoporosis or low bone density. The sources of this information must be identified, and it must be current information from the National Center for Health Statistics, the National Institutes of Health, or the National Osteoporosis Foundation."

The agency is proposing to add new paragraph (d)(4) to § 101.72, which will provide that the mechanism by which calcium, or when appropriate, calcium and vitamin D, reduces the risk of osteoporosis may be optional information in the claim. Thus, new paragraph (d)(4) would read as follows: "The claim may state that the role of adequate calcium intake, or when appropriate, the role of adequate calcium and vitamin D intake, throughout life is linked to reduced risk of osteoporosis through the mechanism of optimizing peak bone mass during adolescence and early adulthood. The phrase "build and maintain good bone health" may be used to convey the concept of optimizing peak bone mass. When reference is made to persons with a family history of the disease, menopausal women, and elderly men and women, the claim may also state that adequate intake of calcium, or adequate

intake of calcium and vitamin D, if applicable, is linked to reduced risk of osteoporosis through the mechanism of slowing the rate of bone loss."

Since many of the amendments FDA is proposing will alter language used in the calcium and osteoporosis or the additional calcium and vitamin D and osteoporosis health claim, FDA is proposing to revise § 101.72(e) to provide model health claims for the calcium and osteoporosis health claim and to add new paragraph (f) to § 101.72 to provide model health claims for the additional calcium and vitamin D and osteoporosis health claim.

The agency invites comments to any or all of the proposed amendments to § 101.72.

VI. Analysis of Economic Impacts

A. Preliminary Regulatory Impact Analysis

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is not a significant regulatory action as defined by the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant economic impact of a rule on small entities. The proposed rule, if finalized, amends the current calcium and osteoporosis health claim language and would require changes to the claim language on products currently bearing the health claim. Thus, the only

mandatory costs of this proposed rule, if finalized, would be the costs to update the current wording of the calcium and osteoporosis health claim on those products that currently bear the claim. Based on FDA's 2001 Food Labeling and Product Survey (FLAPS) (see discussion in section VI.A.2 "Background" of this document), very few products bear the calcium and osteoporosis health claim. Therefore, because of the limited use of the current calcium and osteoporosis health claim, the agency certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $122 million, using the most current (2005) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount and has determined that this proposed rule does not constitute a significant rule under the Unfunded Mandates Reform Act.

1. Need for This Regulation

Current regulations do not permit food producers to claim health benefits for products by linking the intake of vitamin D, when combined with the intake of calcium, with a reduced risk of osteoporosis. However, current regulations do permit food producers to claim health benefits for products by linking calcium intake with a reduced risk of osteoporosis only if they also list the

specific risk factors and at-risk subpopulations for osteoporosis, the mechanism by which calcium reduces the risk of osteoporosis, and the limit of the benefits of dietary calcium at certain levels.

Health claims can inform consumers about diet-disease relationships and encourage producers to produce more healthful foods. This proposed rule would allow producers to make more nutrition information related to osteoporosis available to consumers (linking the intake of calcium and vitamin D to the risk of osteoporosis), while eliminating other information currently required to be given to consumers when claiming health benefits relating to the link between calcium intake and the risk of osteoporosis.

2. Background

Osteoporosis represents a major public health problem in the United States. This disease affects more than 10 million individuals and causes approximately 1.5 million fractures annually. Every year, these lead to 2.6 million physician office visits, 800,000 emergency room visits, and more than 500,000 hospitalizations, and the placement of nearly 180,000 people into nursing homes. The direct care expenditures for osteoporotic fractures alone range from $12 to $18 billion each year (measured in 2002 dollars) (Ref. 4). The indirect health costs, such as pain, suffering, and lost mobility, of osteoporosis are also large. Average calcium and vitamin D intakes are below recommended levels for many consumers (Refs. 4, 49, and 50). Even though many consumers are not achieving recommended intakes of calcium, producers have rarely placed the calcium-osteoporosis health claim on products that qualified for the claim. FDA's 2001 FLAPS (the most recently available data) showed only 1 out of the 87 shelf-stable juice products

surveyed, a fortified orange juice, bearing the calcium osteoporosis health claim. None of the 10 milk products surveyed bore the claim (Ref. 51).

3. Regulatory Options

FDA has identified four regulatory options for this proposed rule: (1) Take no new regulatory action; (2) reduce the required language in the existing calcium-osteoporosis health claim; (3) expand the existing calcium-osteoporosis health claim to include vitamin D; or (4) reduce the required language in the existing calcium osteoporosis health claim and include vitamin D as an option to the claim, as described in this proposed rule.

4. Changes in Market Behavior in Response to Options

This proposed rule, if finalized as proposed, would require that any food manufacturers wishing their products' labels to make the calcium, or calcium and vitamin D, and osteoporosis health claim be redesigned. Labels must be redesigned in order for a food to carry the health claim since information on populations at particular risk for osteoporosis would no longer be required or allowed for the claim (see § 101.72(c)(2)(A) and (c)(2)(B)).

Products that wish to continue making a calcium health claim would not need to reformulate their products under the proposed rule. The nature of the food eligible to make a calcium health claim remains food that meets or exceeds a "high" level of calcium (as defined in § 101.54(b)). Manufacturers wishing to take advantage of the expanded calcium and vitamin D claim may voluntarily choose to reformulate their products. If some producers choose to reformulate their products to take advantage of the calcium and vitamin D health claim, they reveal that they expect the private benefit that the claims give them to exceed the expense of making the claims. If this is not the case, no producer will voluntarily choose to use the claims. Likewise, consumers

who choose to purchase the products with the amended health claims reveal that they value the products more highly than other alternatives, including not purchasing the products.

We consider five potential effects in estimating the relative public health benefits of the options: (1) The extent to which the option encourages producers to use the health claims on their food labels; (2) the extent to which the option encourages producers to reformulate their products to make the health claims; (3) the extent to which the option provides information to consumers; (4) potential risk-risk tradeoffs (where the action taken to reduce the risk posed by one hazard causes an increase in the risk posed by another hazard) with each option; and (5) the availability of information on the relationship between osteoporosis and calcium and vitamin D to consumers who do not consume dairy products.

Producer responses

There are four likely responses to this proposal from producers: (1) Make no changes (i.e., continue not making the calcium or calcium and vitamin D health claim; (2) create new product labels to continue making the calcium health claim (for products already making the existing claim); (3) add the health claims to their products that qualify for the health claims (increase usage of the claim due to the new required wording); and (4) reformulate their products (by fortifying with calcium or vitamin D, for example) to qualify for the health claims.

Several factors affect whether producers choose to use health claims, including the flexibility of the health claims and how appealing the health claims are to consumers. Revising the existing calcium osteoporosis health claim language to make it shorter will make it more appealing to put the health

claims on labels. Package space is limited, so more flexible and shorter claims are easier to use. Also, Wansink, et al. (2004) found that shorter health claims on the front of the package led to more favorable beliefs about the product and a more positive image of the product among consumers (Ref. 52).

Approving a calcium, vitamin D, and osteoporosis health claim should encourage the manufacturers of foods that are eligible for fortification with vitamin D to do so because they will be able to publicize the relationship between vitamin D, calcium, and osteoporosis on their labels. If producers fortify more products with vitamin D, consumers can get more vitamin D in their diet without making changes in their dietary choices.

Consumer responses

Providing information about the relationship between calcium, vitamin D, and osteoporosis on food packages provides a number of benefits to consumers, including: (1) Informing them about the nutrient-disease relationship; (2) helping them identify products that are high in calcium and vitamin D; and (3) helping them make dietary choices that reduce their risk of osteoporosis. The extent to which consumers realize these benefits will depend on the consumers knowledge of the relationship between calcium, vitamin D, and bone health; how many products bear the calcium or calcium and vitamin D health claims; how many consumers read the health claims; and how much they change their behavior to include such products in their diets. There is evidence that consumers who read nutrition information on packages eat healthier diets (Refs. 53 and 54). However, there is a great deal of uncertainty about how much consumers change their behavior in response to label information.

Risk-risk tradeoffs

A potential concern is that allowing these osteoporosis health claims on juice drinks will result in consumers switching away from milk to juice drinks, which are higher in calories, for dietary sources of calcium and vitamin D. Table 1 of this document presents the caloric and nutrient profile of non-fat and low-fat milk products and an orange juice drink product as reported in the USDA National Nutrient Database for Standard Reference. Orange juice drinks are higher in calories and contain less of some important nutrients than either non-fat or low-fat milk (table 1 of this document).

TABLE 1: PROFILES OF SELECTED NUTRIENTS IN NON-FAT AND LOW-FAT MILK AND ORANGE JUICE DRINK (PER 8-OUNCE SERVING)

Nutrient	(1) Orange juice drink	(2) Non-fat Milk (Skim), with added vitamin A	(3) Low Fat Milk (1%), with added vitamin A
Energy, kcal	134	83	102
Protein, g	0.5	8.25	8.22
Total Fat, g	0	0.2	2.37
Saturated Fat, g	0	0.286	1.545
Carbohydrate, g	33.36	12.14	12.18
Total Dietary Fiber, g	0.5	0	0
Total Sugars, g	23.29	12.46	12.69
Calcium, mg	5	306	290
Iron, mg	0.27	0.07	0.07
Magnesium, mg	7	27	27
Phosphorus, mg	10	247	232
Potassium, mg	104	382	366
Sodium, mg	5	103	107
Zinc, mg	0.05	1.03	1.02
Copper, mg	0.045	0.032	0.024
Manganese, mg	0.017	0.007	0.007
Selenium, mcg	0	7.6	8.1
Vitamin C, mg	37.3	0	0
Thiamin, mg	0.945	0.11	0.049
Riboflavin, mg	1.07	0.446	0.451
Niacin, mg	12.44	0.23	0.227
Pantothenic acid, mg	0.149	0.874	0.881
Vitamin B–6, mg	1.244	0.091	0.09
Folate, mcg	10	12	12
Vitamin B–12, mcg	0	1.3	1.07
Vitamin A, IU	109	499	478
Vitamin D, IU	0	101.46	126.77

TABLE 1: PROFILES OF SELECTED NUTRIENTS IN NON-FAT AND LOW-FAT MILK AND ORANGE JUICE DRINK (PER 8-OUNCE SERVING)—Continued

Nutrient	(1) Orange juice drink	(2) Non-fat Milk (Skim), with added vitamin A	(3) Low Fat Milk (1%), with added vitamin A
Cholesterol, mg	0	5	12

The likelihood of consumers switching from non-fat or low-fat milk or to higher caloric juice drinks because of this rule is expected to be small because non-fat and low-fat milk and juice drinks that are eligible can already make the existing calcium and osteoporosis health claim. Permitting the same set of products to make the proposed, simpler calcium and osteoporosis health claim should not change the relative appeal of the claim to producers of one type of beverage over another. The allowance of the new calcium and vitamin D osteoporosis health claim could expand the set of products making an osteoporosis claim; however, the relative appeal of the new claim (calcium and vitamin D) to producers of non-fat and low-fat milk and juice drinks should be similar to the appeal of the existing calcium osteoporosis claim.

There is little evidence to support that consumers would switch from non-fat or low-fat milk to juice drinks as a result of this proposed rule. As stated in the Surgeon General's report on bone health and osteoporosis, consuming adequate levels of calcium and vitamin D throughout life are critically important to an individual's bone health. However, the report's review of national surveys suggests that the average calcium intake of individuals is far below the levels recommended for optimal bone health. One reason cited by the report for these low levels of calcium intake relates to current lifestyle and food preferences, which have resulted in reduced intake of dairy products and other naturally occurring calcium-rich foods. The report also posits that for some individuals lactose intolerance[3] may also play a role in not consuming

[3]Lactose intolerance is a condition in which individuals cannot metabolize lactose, the main sugar found in milk and other calcium-rich dairy products. Information in the Surgeon

adequate levels of calcium. Given this information on the current preference and tolerance for dairy products, expanding the calcium and osteoporosis health claim to include vitamin D as a result of this proposed rule should only lead to an increase in the overall consumption of these essential, under consumed nutrients.

In addition, according to the American Beverage Association, U.S. sales of calcium-fortified orange juice has grown dramatically over recent years, reaching nearly $1 billion in 2003 (Ref. 55), while overall sales of juice have not grown. Therefore, FDA expects that the nutritional profile of diets would most likely improve as a consequence of changes in consumption resulting from this proposed rule. Switching from unfortified to fortified juices would increase needed consumption of calcium and vitamin D.

5. Benefits and Costs of Regulatory Options

The simplification of the current health claim for calcium and osteoporosis, along with the additional proposed health claim for calcium, vitamin D, and osteoporosis should increase and expand the current usage of the health claim and therefore improve the U.S. population's intake of these two important nutrients. Therefore, all of the options considered below would improve public health relative to the baseline of taking no new regulatory action. In our analysis of the benefits and costs of the options, we compare the benefits and costs of each option with each other option based on their relative effects on consumer and producer behavior.

Option 1: Take no new regulatory action

This option would result in no change to the current situation. This is the baseline for comparison of options and entails no costs or benefits.

General's report on bone health and osteoporosis indicates that an estimated 30 to 50 million Americans are affected by lactose intolerance, although to varying degrees.

Option 2: Reduce the required language in the existing calcium osteoporosis health claim.

Compared with Option 1, this option would increase the appeal of the claim for producers, increase the use of the claim on products, and thereby provide consumers with more information on the calcium and osteoporosis diet-disease relationship. It could encourage more reformulation of products to fortify with calcium than has occurred with the existing claim. Like Option 1, this option provides consumers with no information about the relationship of vitamin D to osteoporosis.

With this option, manufacturers of some products making the current calcium and osteoporosis health claim may have to re-label their products to reflect the updated wording provided by the proposed claim. The potential costs associated with a required label change will vary depending on when the new effective compliance date is established. Table 2 of this document shows the possible range of costs by product type of having to re-label to be in compliance with the revised calcium and osteoporosis health claim. The product re-labeling costs were estimated using the FDA Labeling Cost Model (Ref. 56). The costs of re-labeling included are administrative, graphic, prepress, engraving, and inventory costs. Re-labeling costs are shown for both a 12 month and 24 month compliance period.

TABLE 2: COST OF LABEL CHANGES FOR OPTION 2

		12 months to comply, cost per label SKU			24 months to comply, cost per label SKU		
NAICS Codes	Product	Low Cost	Med Cost	High Cost	Low Cost	Med Cost	High Cost
311421 311411	Fruit Juices	$7,478	$10,186	$15,282	$5,455	$7,595	$11,897
311514 311511	Non-fat and Low-fat Milk, fluid, dry, powered, condensed, flavored	$11,216	$14,086	$20,437	$7,127	$9,236	$14,327
311513	Low-fat Cheese, multiple types	$6,611	$8,759	$13,758	$5,106	$6,999	$11,489
311511	Yogurt-like products	$4,554	$6,490	$10,857	$4,140	$5,900	$9,880
325412	Dietary Supplements	$9,728	$13,345	$22,834	$8,540	$11,739	$20,266
Average cost of label change regardless of product type		$7,917	$10,573	$16,633	$6,074	$8,294	$13,572

Option 3: Expand the existing calcium and osteoporosis health claim to include vitamin D

Failing to shorten the existing calcium and osteoporosis health claim will not make the health claim as appealing to producers and consumers as Option 2, leading to less claim use and reformulation and less information provided to consumers than Option 2. This option would provide consumers with more information on vitamin D than Option 2, should producers decide to voluntarily re-label and/or reformulate their products to make use of the added vitamin D language.

Option 4: Reduce the required language in the existing calcium and osteoporosis health claim and include vitamin D as an option to the claim, as described in this proposed rule

Like Option 2, this option would increase the appeal of the calcium and osteoporosis health claim for producers and thereby provide consumers with more information on the calcium and osteoporosis diet-disease relationship. Also like Option 2, producers of products with existing calcium and osteoporosis health claim labeling will have to revise their labeling in order to comply with the revised claim language. Like Option 3, this option would provide consumers with more information on vitamin D than Option 2 because the new, simplified calcium and osteoporosis health claim can now contain information about vitamin D as well. It could also encourage more reformulation of products to fortify with vitamin D than would Option 2 and as many products to fortify with calcium as Option 2.

Summary

FDA is unable to quantify the benefits of this proposed rule due to uncertainty about the degrees of changes in consumer and producer behavior.

However according to information compiled in the Surgeon General's report on bone health and osteoporosis, there are about 1.5 million osteoporotic fractures in the United States each year that carry annual direct care expenditures of $12 to $18 billion per year (2002 dollars). These fractures cause more than half a million hospitalizations, over 800,000 emergency room encounters, more than 2.6 million physician office visits, and the placement of nearly 180,000 individuals into nursing homes annually (Ref. 4). The direct costs of other complications from osteoporosis, and the indirect costs of these fractures and other osteoporotic ailments (e.g., the value of functional disability to the patient, the value of the pain and suffering to the patient, the costs experienced by the care giver) if calculated, would add substantially to the annual costs of this disease. Any increase in calcium and vitamin D intake by consumers insufficient in these nutrients as a result of this proposed rule could possibly lower the incidence of osteoporosis and therefore the annual costs associated with the disease.

Table 3 of this document provides a summary of the effects of the rule, and which options create the smallest and largest behavior changes for consumers and producers. All options should produce positive net benefits, with the largest net benefit arising from Option 4, the proposed rule. With Option 4, the largest number of products and labels would change, leading to the largest reduction in the risk of osteoporosis.

TABLE 3: SUMMARY OF EFFECTS OF OPTIONS

Effect	Largest effect	Smallest effect
Encouraging producer use of the claims	Option 4	Option 1
Encouraging fortification	Option 4	Option 1
Informing consumers	Option 4	Option 1

TABLE 3: SUMMARY OF EFFECTS OF OPTIONS—Continued

Effect	Largest effect	Smallest effect
Informing consumers who do not buy dairy products about alternative food sources for vitamin D	Option 4	Option 1

B. Small Entity Analysis (or Initial Regulatory Flexibility Analysis)

FDA has examined the economic implications of this proposed rule as required by the Regulatory Flexibility Act (5 U.S.C. 601–612). If a rule has a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would lessen the economic effect of the rule on small entities consistent with statutory objectives. FDA does not believe that this proposed rule will have a significant economic impact on a substantial number of small entities because the only mandatory costs of this rule are the costs to update the current wording of the calcium osteoporosis health claim for manufacturers of products that currently make the claim and wish to continue doing so. Also previously mentioned, FDA's 2001 Food Labeling and Product Survey showed only 1 out of 87 shelf-stable juice products surveyed bore the current calcium and osteoporosis health claim while none of the 10 milk products surveyed bore the claim. This implies that not many products eligible to bear the current claim would need to be re-labeled as a result of this proposed rule.

In addition, FDA establishes uniform compliance dates for final food labeling regulations in 2-year intervals. Therefore, companies whose products currently make the calcium and osteoporosis health claim and wish to continue doing so will have between 1 and 2 years to use existing label inventory and expense the costs of designing revised labeling. FDA estimates that on average, the cost to re-label a product according to the revised health

claim language will be $7,900 to $16,600 per product if the compliance period is 12 months; and $6,100 to $13,600 per product if the compliance period is 24 months. FDA requests comment on whether this rule will have a significant impact on a substantial number of small entities. Manufacturers that wish to begin using the revised calcium and osteoporosis health claim or the new calcium, vitamin D, and osteoporosis health claim will only do so if the benefits of labeling their products to inform consumers of the claim outweigh the costs of doing so.

VII. Environmental Impact

The agency has determined under 21 CFR 25.32(p) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Paperwork Reduction Act

FDA concludes that the labeling provisions of this proposed rule are not subject to review by the Office of Management and Budget because they do not constitute a "collection of information" under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). Rather the food labeling health claim on the association between calcium only, or calcium and vitamin D, and reduced risk osteoporosis is a "public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public" (5 CFR 1320.3(c)(2)).

IX. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule, if finalized as proposed, has a preemptive effect on State law. Section 4(a) of the Executive order requires agencies to "construe * * * a Federal Statute to

preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute." Section 403A of the act (21 U.S.C. 343–1) is an express preemption provision. Section 403A(a)(5) of the act (21 U.S.C. 343–1(a)(5)) provides that: "***no State or political subdivision of a State may directly or indirectly establish under any authority or continue in effect as to any food in interstate commerce—***(5) any requirement respecting any claim of the type described in section 403(r)(1) of the act made in the label or labeling of food that is not identical to the requirement of section 403(r) * * *." Currently, this provision operates to preempt States from imposing health claim labeling requirements concerning calcium and vitamin D and reduced risk of osteoporosis because no such requirements had been imposed by FDA under section 403(r) of the act. This proposed rule, if finalized as proposed, would amend existing food labeling regulations to add vitamin D to the authorized health claim for calcium and a reduced risk of osteoporosis and would simplify the claim language. Although any final rule would have a preemptive effect in that it would preclude States from promulgating any health claim labeling requirements for calcium or calcium and vitamin D and a reduced risk of osteoporosis that are not identical to those that would be required by a final rule, this preemptive effect is consistent with what Congress set forth in section 403A of the act. Section 403A(a)(5) of the act displaces both state legislative requirements and state common law duties. *Medtronic* v. *Lohr*, 518 U.S. 470, 503 (1996) (Breyer, J., concurring in part and concurring in judgment); id. at 510 (O'Connor, J., joined by Rehnquist, C.J., Scalia, J., and Thomas, J., concurring in part and

dissenting in part); *Cipollone* v. *Liggett Group, Inc.*, 505 U.S. 504, 521 (1992) (plurality opinion); id. at 548–49 (Scalia, J., joined by Thomas, J., concurring in judgment in part and dissenting in part).

FDA believes that the preemptive effect of this proposed rule, if finalized as proposed, is consistent with Executive Order 13132. Section 4(e) of the Executive order provides that "when an agency proposes to act through adjudication or rulemaking to preempt State law, the agency shall provide all affected State and local officials notice and an opportunity for appropriate participation in the proceedings." FDA provided the States with an opportunity for appropriate participation in this rulemaking when it sought input from all stakeholders on February 17, 2006, when FDA's Division of Federal and State Relations provided notice via fax and e-mail transmission to State health commissioners, State agriculture commissioners, food program directors, and drug program directors as well as FDA field personnel of FDA's potential amendment to the health claim regulation authorizing health claims for calcium and osteoporosis (§ 101.72). The notice provided the States with further opportunity for input on the rule. It advised the States of FDA's possible action and encouraged the States and local governments to review the notice and to provide any comments to the docket (Docket No. 2004P–0294), until March 2, 2006. FDA received no comments in response to the notice. FDA is also providing an opportunity for State and local officials to comment on this proposed rule.

In conclusion, the agency has determined that the preemptive effects of this proposed rule are consistent with Executive Order 13132.

X. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

XI. References

The following references have been placed on display in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register.**)

1. The Beverage Institute for Health and Wellness, "Petition for Vitamin D, Calcium and Osteoporosis," (Docket No. 2004P–0464, CP1), July 12, 2004.

2. Osteoporosis, Prevention, Diagnosis, and Therapy, National Institutes of Health Consensus Statement, 17(1):1–45, March 27–19, 2000.

3. National Osteoporosis Foundation, America's Bone Health: The State of Osteoporosis and Low Bone Mass, 2002, *http://www.nof.org/advocacy/prevelence/index.htm.*

4. Bone Health and Osteoporosis: A Report of the Surgeon General, Rockville, MD: United States Department of Health and Human Services, Office of the Surgeon General, 2004.

5. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine, "Dietary Reference Intakes for

Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride," Chapter 4, National Academy Press, Washington, DC, 1997.

6. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine, "Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride," Chapter 7, National Academy Press, Washington, DC, 1997.

7. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine, "Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride," Chapter 3, *National Academy Press*, Washington, DC, 1997.

8. Bialostosky, K., J. Wright, J. Kennedy-Stephenson, et al., "Dietary Intake of Macronutrients Micronutrients and Other Dietary Constituents: United States 1988–1994," *National Center for Health Statistics, Vital Health Statistics* 11(245), Tables 93 and 94, 2002.

9. Erwin, R. E., J. D. Wright, and D. Read-Gillette, "Prevalence of Leading Types of Dietary Supplements Used in the Third National Health and Nutrition Examination Survey, 1988–1994," *National Center for Health Statistics, Advance Data from Vital and Health Statistics*; no. 349, Hyattsville, MD: 2004.

10. Rajakumar, K., "Vitamin D, Cod Liver Oil, Sunlight and Rickets: A Historical Perspective," *Pediatrics*, 112:132–135, 2003.

11. Memorandum to the record, Determination of Amounts of Vitamin D and Calcium in Common Dietary Supplement Products, prepared by Jillonne H. Kevala, FDA, February 22, 2006.

12. Ervin, R. B., C. Y. Wang, J. D. Wright, et al., "Dietary Intake of Selected Minerals for the United States Population: 1999–2000," *National Center for Heath Statistics, Advance Data from Vital and Health Statistics*; no. 341 Hyattsville, MD: 2004.

13. Prentice, A., J-P. Bonjour, F. Branca, et al., "PASSCLAIM—Bone Health and Osteoporosis," *European Journal of Nutrition*, 42(Suppl 1):1/28–1/49, 2003.

14. H. F. DeLuca, "Overview of General Physiologic Features and Functions of Vitamin D," *American Journal of Clinical Nutrition*, 80(suppl):1689S–1696S, 2004.

15. William F. Ganong, "Hormonal Control of Calcium Metabolism and the Physiology of Bone," Chapter 21 in *Review of Medical Physiology*, 21st ed., New York, McGraw-Hill Companies, 2003.

16. R. P. Heaney, "The Importance of Calcium, Intake for Lifelong Skeletal Health," *Calcified Tissue International*, 70:70–73, 2002.

17. "Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements," Rockville, MD: (*http://www.cfsan.fda.gov/~dms/ssaguide.html*), December 1999.

18. Aloia, J.F., A. Vaswani, J. D. Yeh, et al., "Calcium Supplementation With and Without Hormone Replacement Therapy to Prevent Postmenopausal Bone Loss," *Annals of Internal Medicine*, 120:97–103, 1994.

19. Baeksgaard, L., K. P. Andersen, and L. Hyldstrup, "Calcium and Vitamin D Supplementation Increases Spinal BMD in Healthy, Postmenopausal Women," *Osteoporosis International*, 8:255–260, 1998.

20. Chapuy, M. C., M. E. Arlot, F. Duboeuf, et al., "Vitamin D_3 and Calcium to Prevent Hip Fractures in Elderly Women", *The New England Journal of Medicine,*" 327:1637–1642, 1992.

21. Chapuy, M. C., M.E. Arlot, P. D. Delmas, et al., "Effect of Calcium and Cholecalciferol Treatment for Three Years on Hip Fractures in Elderly Women," *British Medical Journal*, 308:1081–1082, 1994.

22. Dawson-Hughes, B., G. E. Dallal, G.E., Krall, E.A., Harris, S., Sokoll, L.J., and G. Falconer, "Effect of Vitamin D Supplementation on Wintertime and Overall Bone Loss in Healthy Postmenopausal Women," *Annuals of Internal Medicine*, 115:505–512, 1991.

23. Dawson-Hughes, B., S. S. Harris, E. A. Krall, et al., "Effect of Calcium and Vitamin D Supplementation on Bone Density in Men and Women 65 Years of Age or Older," *The New England Journal of Medicine*, 337:670–676, 1997.

24. Dawson-Hughs, B., S. S. Harris, E. A. Krall, et al., 2000 "Effect of Withdrawal of Calcium and Vitamin D Supplements on Bone Mass in Elderly Men and Women," *American Journal of Clinical Nutrition*, 72:745–750, 2000.

25. Grados, F., M. Brazier, S. Kamel, et al., "Effects on Bone Mineral Density of Calcium and Vitamin D Supplementation in Elderly Women With Vitamin D Deficiency," *Joint Bone Spine*, 70:203–208, 2003.

26. Krieg, M. A., A. F. Jacquet, M. Bremgartner, et al., "Effect of Supplementation with Vitamin D_3 and Calcium on Quantitative Ultrasound of Bone in Elderly Institutionalized Women: A Longitudinal Study," *Osteoporosis International*, 9:483–488, 1999.

27. Orwoll, E. S., S. K. Oviatt, M. R. McClung, et al., "The Rate of Bone Mineral Loss in Normal Men and the Effects of Calcium and Cholecalciferol Supplementation," *Annuals of Internal Medicine*, 112:29–34, 1990.

28. Prestwood, K. M., D. L. Thompson, A. M. Kenny, et al., "Low Dose Estrogen and Calcium Have an Additive Effect on Bone Resorption in Older Women," *Journal of Clinical Endocrinology Metabolism*, 84:179–183, 1999.

29. Sosa, M., P. Láinez, A. Arbelo, et al., "The Effect of 25-dihydroxyvitamin D on the Bone Mineral Metabolism of Elderly Women with Hip Fracture," *Rheumatology*, 39:1263–1268, 2000.

30. Jackson, R. D., et al., "Calcium Plus Vitamin D Supplementation and the Risk of Fractures, The Women's Health Initiative," *The New England Journal of Medicine*, 354:669–683, 2006.

31. Spilker, B. in Guide to Clinical Trials, Philadelphia, PA: Lippincott Williams & Wilkins, 2000, p. 59–64.

32. Cumming, R. G., and M. C. Nveitt, "Calcium for Prevention of Osteoporotic Fractures in Postmenopausal Women," *Journal of Bone Mineral Research*, 12:1321–1329, 1997.

33. Ensrud, K. R., T. Duong, J. A. Cauley, et al., "Low Fractional Calcium Absorption Increases the Risk for Hip Fracture in Women with Low Calcium Intake," *Annuals of Internal Medicine*, 132:345–353, 2000.

34. Hannan, M. T., D. T. Felson, B. Dawson-Hughes, et al., "Risk Factors for Longitudinal Bone Loss in Elderly Men and Women: The Framingham Osteoporosis Study," *Journal of Bone Mineral Research*, 15:710–720, 2000.

35. Ilich, J. Z., M. Skugor, T. Hangartner, et al., "Relation of Nutrition, Body Composition and Physical Activity to Skeletal Development: A Cross-Sectional Study in Preadolescent Females," *Journal of the American College of Nutrition*, 17:136–147,1998.

36. Kardinaal, A. F. M., A. Ando, P. Charles, et al., "Dietary Calcium and Bone Density in Adolescent Girls and Young Women in Europe," *Journal of Bone Mineral Research*, 14:583–592, 1999.

37. Kristinsson, J. Ö., Ö. Valdimarsson, G. Sigurdsson, et al., "Serum 25-hydorxyvitamin D Levels and Bone Mineral Density in 16-20-Year-Old Girls: Lack of Association," *Journal of Internal Medicine*, 243:381–388, 1998.

38. Lamberg-Allardt, C. J. E., T. A. Outila, M. U. M. Kärkkäinen, et al., "Vitamin D Deficiency and Bone Health in Healthy Adults in Finland: Could this be a Concern in Other Parts of Europe?," *Journal of Bone Mineral Research*, 16:2066–2073, 2001.

39. Oliveri, M. B., A. Wittich, C. Mautalen, et al., "Peripheral Bone Mass is Not Affected by Winter Vitamin D Deficiency in Children and Young Adults from Ushuaia," *Calcified Tissue International*, 67:220–224, 2000.

40. Flegal, K. M., "Evaluating Epidemiologic Evidence of the Effects of Food and Nutrient Exposures," *American Journal of Clinical Nutrition*, 69:1339S–1344S, 1999.

41. Reddy, M. B. and M. Love, "The Impact of Food Processing on the Nutritional Quality of Vitamins and Minerals," *Advances in Experimental Medicine and Biology*, 459:99–106, 1999.

42. Sempos, C. T., K. Liu, and N.D. Ernst, "Food and Nutrient Exposures: What to Consider When Evaluating Epidemiologic Evidence," *American Journal of Clinical Nutrition*, 69:1330S–1338S, 1999.

43. National Institutes of Health, Office of the Director, "NIH Consensus Statement, Optimal Calcium Intake," vol. 12, No. 4, June 6–8, 1994.

44. Cummings, S. R. and L. J. Melton, III, "Epidemiology and Outcomes of Osteoporotic Fractures," *The Lancet*, 359:1761–1767, 2002.

45. Zingmond, D. S. and L. J. Melton, 3rd, and S. L. Silverman. "Increasing Hip Fracture Incidence in California Hispanics, 1983 to 2000," Osteoporosis International, 8:603–610, 2004.

46. Specker B. L., L. Mulligan, and M. L. Ho, "Longitudinal Study of Calcium Intake, Physical Activity, and Bone Mineral Content in Infants 6-18 Months of Age," *Journal of Bone Mineral Research*, 4:569–576, 1999.

47. Specker B., and T. Binkley, "Randomized Trial of Physical Activity and Calcium Supplementation on Bone Mineral Content in 3- to 5-Year-Old Children," *Journal of Bone Mineral Research*, 18:885–892, 2003.

48. Levy, A., Food and Drug Administration, Center for Food Safety and Applied Nutrition, Division of Market Studies, "Summary Report on Health Claims Focus Groups," June 15, 1995.

49. Calvo, M. S., S. J. Whiting, and C. N. Barton, "Vitamin D Fortification in the United States and Canada: Current Status and Data Needs," *American Journal of Clinical Nutrition*, 80(suppl):1710S–1716S, 2004.

50. Moore, C., M. M. Murphy, D. R. Keast, et al., "Vitamin D Intake in the United States," *Journal of the American Dietetic Association*, 104(6):980–983, 2004.

51. U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Nutritional Products, Labeling, and Dietary Supplements, "Food Label and Package Survey 2000–2001," (*http://www.cfsan.fda.gov/~dms/lab-flap.html*), August 2004.

52. Wansink B., Sonka, S.T. and C.M. Hasler, "Front-Label Health Claims: When Less is More," *Food Policy*, 29(6):659–667, 2004.

53. Kim, S., R. M. Nayga, Jr., and O. Capps Jr., "The Effect of Food Label Use on Nutrient Intakes: An Endogenous Switching Regression Analysis," *Journal of Agricultural and Resource Economics*, 25(1):215–231, 2000.

54. Neuhouser, M. L., A. R. Kristal, and R. E. Patterson, "Use of Food Nutrition Labels Associated With Lower Fat Intake," *Journal of the American Dietetic Association*, 99(1):45–50, 53, 1999.

55. American Beverage Association, Press Release, September 17, 2004, (*http://www.ameribev.org/news-detail/index.aspx?nid=32*).

56. "Food and Drug Administration Labeling Cost Model," Health, Social, and Economics Research, Research Triangle Park, NC, January 2003.

List of Subjects in 21 CFR Part 101

Food labeling, Nutrition, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under the authority delegated to the Commissioner of the Food and Drugs, and redelegated to the Deputy Director for Regulatory Affairs, it is proposed that 21 CFR part 101 be amended as follows:

PART 101—FOOD LABELING

1. The authority citation for 21 CFR part 101 continues to read as follows:

Authority: 15 U.S.C. 1453, 1454, 1455; 21 U.S.C. 321, 331, 342, 343, 348, 371; 42 U.S.C. 243, 264, 271.

2. Section 101.72 is revised to read as follows:

§ 101.72 Health claims: calcium, vitamin D, and osteoporosis.

(a) *Relationship between calcium, vitamin D, and osteoporosis.* An inadequate intake of calcium or calcium and vitamin D contributes to low peak bone mass, which has been identified as one of many risk factors in the development of osteoporosis. Peak bone mass is the total quantity of bone present at maturity, and experts believe that it has the greatest bearing on whether a person will be at risk of developing osteoporosis and related bone fractures later in life. Another factor that influences total bone mass and susceptibility to osteoporosis is the rate of bone loss after skeletal maturity. Vitamin D is required for normal absorption of calcium and to prevent the occurrence of high serum parathyroid hormone (PTH) concentration, which stimulates mobilization of calcium from the skeleton and can lower bone mass. Calcium, along with vitamin D and several other nutrients, is required for normal bone mineralization. While vitamin D is required for optimal bone mineralization, it is more effective when calcium intake is adequate. An adequate intake of calcium and vitamin D is thought to exert a positive effect during adolescence and early adulthood in optimizing the amount of bone that is laid down. However, the upper limit of peak bone mass is genetically determined. The mechanism through which adequate intakes of calcium and vitamin D and optimal peak bone mass reduce the risk of osteoporosis is thought to be as follows. All persons lose bone with age. Hence, those with higher bone mass at maturity take longer to reach the critically reduced mass at which bones can fracture easily. The rate of bone loss after skeletal maturity also influences the amount of bone present at old age and can influence an individual's risk of developing osteoporosis. Maintenance of adequate intakes

of calcium and vitamin D later in life is thought to be important in reducing the rate of bone loss particularly in the elderly and in women during the first decade following menopause, but a significant protective effect is also seen among men and younger women.

(b) *Significance of calcium or calcium and vitamin D.* Adequate calcium intake, or adequate calcium and vitamin D intake, is not the only recognized risk factor in the development of osteoporosis, which is a multifactorial bone disease. Maintenance of adequate calcium and vitamin D intakes throughout life is necessary to achieve optimal peak bone mass and to reduce the risk of osteoporosis in later life. However, vitamin D is most effective in this regard when calcium intake is adequate. Increasing intake of calcium has been shown to have beneficial effects on bone health independent of dietary vitamin D.

(c) *Requirements.* (1) All requirements set forth in § 101.14 shall be met.

(2) *Specific requirements*—(i) *Nature of the claim.* A health claim associating calcium or, when appropriate, calcium and vitamin D with a reduced risk of osteoporosis may be made on the label or labeling of a food described in paragraphs (c)(2)(ii) and, (d)(1) of this section, provided that:

(A) The claim makes clear the importance of adequate calcium intake, or when appropriate, adequate calcium and vitamin D intake, throughout life, in a healthful diet along with physical activity, are essential to reduce osteoporosis risk. The claim does not imply that adequate calcium intake, or when appropriate, adequate calcium and vitamin D intake, is the only recognized risk factor for the development of osteoporosis;

(B) The claim does not attribute any degree of reduction in risk of osteoporosis to maintaining an adequate dietary calcium intake, or when appropriate, an adequate dietary calcium and vitamin D intake, throughout life.

(ii) *Nature of the food.* (A) The food shall meet or exceed the requirements for a "high" level of calcium as defined in § 101.54(b);

(B) The calcium content of the product shall be assimilable;

(C) Dietary supplements shall meet the United States Pharmacopeia (U.S.P.) standards for disintegration and dissolution applicable to their component calcium salts, except that dietary supplements for which no U.S.P. standards exist shall exhibit appropriate assimilability under the conditions of use stated on the product label;

(D) A food or total daily recommended supplement intake shall not contain more phosphorus than calcium on a weight per weight basis.

(d) *Optional information.* (1) The claim may include the term "vitamin D" if the food meets or exceeds the requirements for a "high" level of vitamin D as defined in § 101.54(b);

(2) The claim may include information from paragraphs (a) and (b) of this section.

(3) The claim may include information on the number of people in the United States who have osteoporosis or low bone density. The sources of this information must be identified, and it must be current information from the National Center for Health Statistics, the National Institutes of Health, or the National Osteoporosis Foundation.

(4) The claim may state that the role of adequate calcium intake, or when appropriate, the role of adequate calcium and vitamin D intake, throughout life is linked to reduced risk of osteoporosis through the mechanism of optimizing peak bone mass during adolescence and early adulthood. The phrase "build and maintain good bone health" may be used to convey the concept of optimizing peak bone mass. When reference is made to persons with

a family history of the disease, menopausal women, and elderly men and women, the claim may also state that adequate intake of calcium or adequate intake of calcium and vitamin D, if applicable, is linked to reduced risk of osteoporosis through the mechanism of slowing the rate of bone loss.

(e) *Model health claims.* The following model health claims may be used in food labeling to describe the relationship between calcium and osteoporosis:

Physical activity and adequate calcium throughout life, as part of a well-balanced diet, may reduce the risk of osteoporosis.

Adequate calcium as part of a healthful diet, along with physical activity, may reduce the risk of osteoporosis in later life.

(f) *Model additional health claims for calcium and vitamin D.* The following model health claims may be used in food labeling to describe the relationship between calcium, vitamin D, and osteoporosis:

Physical activity and adequate calcium and vitamin D throughout life, as part of a well-balanced diet, may reduce the risk of osteoporosis.

Adequate calcium and vitamin D as part of a healthful diet, throughout life along with physical activity, may reduce the risk of osteoporosis in later life.

Dated: 12/18/06
December 18, 2006.

Michael M. Landa,
Deputy Director,
Regulatory Affairs,
Center for Food Safety and Applied Nutrition

[FR Doc. 06–????? Filed ??–??–06; 8:45 am]

BILLING CODE 4160–01–S

CERTIFIED TO BE A TRUE COPY OF THE ORIGINAL